

**TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371**

ATTORNEY'S DOCKET NUMBER

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10/030600

INTERNATIONAL APPLICATION NO.
PCT/FR00/01966

INTERNATIONAL FILING DATE
7 July 2000

PRIORITY DATE CLAIMED
9 July 1999

TITLE OF INVENTION:

PREPARATION OF 2-(2-ARYLMORPHOLIN-2-YL)ETHANOL DERIVATIVES AND INTERMEDIATES

APPLICANT(S) FOR DO/EO/US

AULOMBARD, Alain; BERNON, Françoise; BONNEFOY, Sabrina; BURGOS, Alain; CABOS, Claude; and LUCAS, Eric

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1)).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☒ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application.
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An unexecuted oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.

☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:

Citation of References

Information Disclosure Statement by Applicant (Form PTO-1449)

[illegible]

531 Rec'd PCT 09 JAN 2002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Filing under 35 U.S.C. § 371
Corresponding to International
Application No.: PCT/FR00/01966

Applicants: AULOMBARD, Alain,
BERNON, Françoise, BONNEFOY, Sabrina,
BURGOS, Alain, CABOS, Claude and
LUCAS, Eric

International Filing Date: July 7, 2000
For: PREPARATION OF 2-(2-
ARYLMORPHOLIN-2-YL)ETHANOL
DERIVATIVES AND INTERMEDIATES

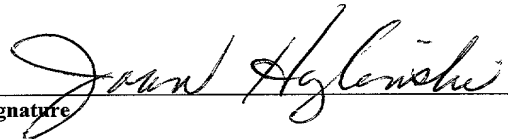
CERTIFICATE UNDER 37 C.F.R. 1.10

Express Mail Label Number: EL676470323US

Date of Deposit: January 9, 2002

I hereby certify that this paper is being deposited with the
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Commissioner for Patents
Box PCT
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Washington, DC 20231

Dear Sir:

PRELIMINARY AMENDMENT

Please amend the above-identified application as follows:

In the Specification:

Please amend the specification as follows:

After the claims, please insert the following Abstract as new page 108 (a copy of
which is enclosed herewith for the examiner's convenience).

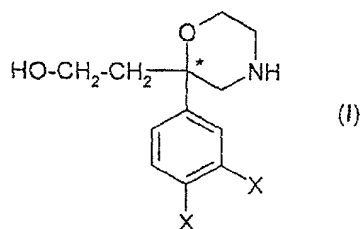
ABSTRACT

The invention relates to a process for the preparation of substituted
2-(2-arylmorpholin-2-yl)ethanol derivatives.

In the Claims:

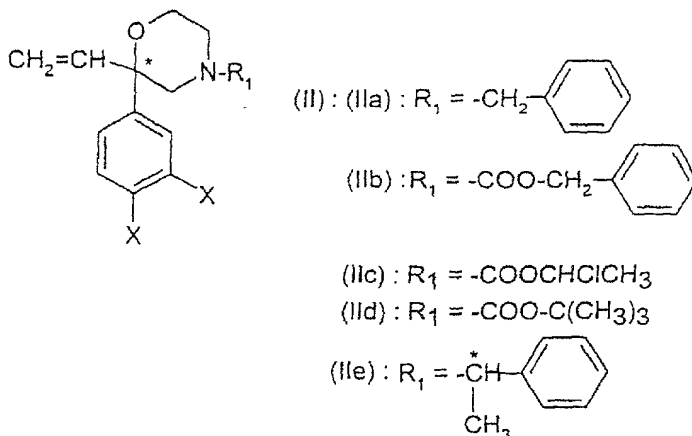
Please amend claims 1-16 and add new claims 32-34 as follows before calculating the
filing fee for the above-identified application.

1. (amended) A process for the preparation of a compound, in the enantiomerically pure form,
of formula:

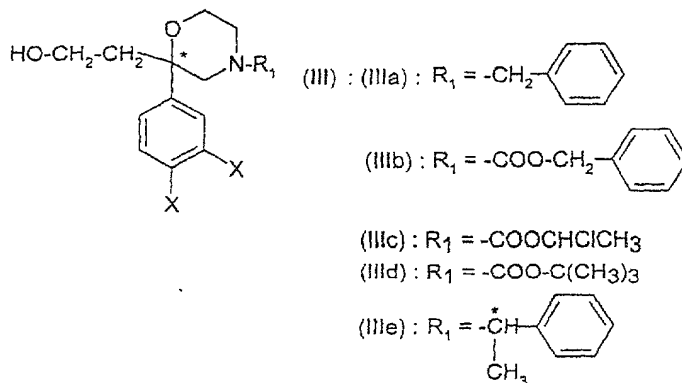


in which X represents a halogen atom, of its salts with inorganic or organic acids or of its salts with optically active organic acids wherein:

a) a compound, in the racemic form, in the form of a mixture of diastereoisomers or in the enantiomerically pure form, of formula:

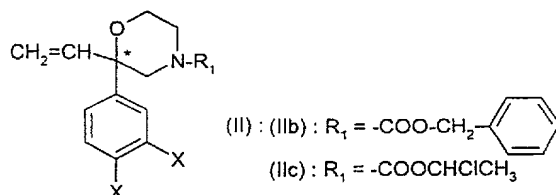


in which X is as defined for a compound of formula (I) and R_1 represents an N-protecting group chosen from a benzyl group, a benzyloxycarbonyl group, a 1-chloroethyloxycarbonyl group, a *tert*-butyloxycarbonyl group or an α -methylbenzyl group, is converted to a compound, in the racemic form, in the form of a mixture of diastereoisomers or in the enantiomerically pure form, of formula:

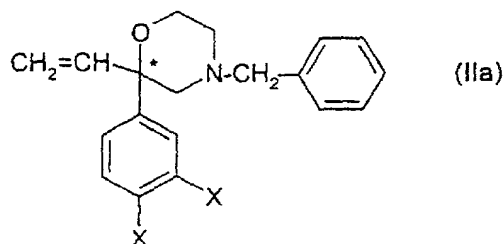


- b) the compound of formula (III) thus obtained is deprotected;
- c) if appropriate, when the compound of formula (I) thus obtained is in the racemic form, the enantiomers are separated, and, optionally, the enantiomerically pure compound of formula (I) is converted to one of its salts with inorganic or organic acids.

2. (amended) The process as claimed in claim 1 wherein a compound, in the enantiomerically pure form or in the racemic form, of formula:

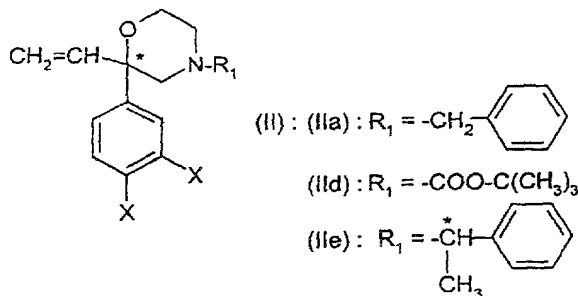


in which X represents a halogen atom and R_1 represents a benzyloxycarbonyl group or a 1-chloroethyloxycarbonyl group, is prepared by reaction of a compound, in the enantiomerically pure form or in the racemic form, of formula:

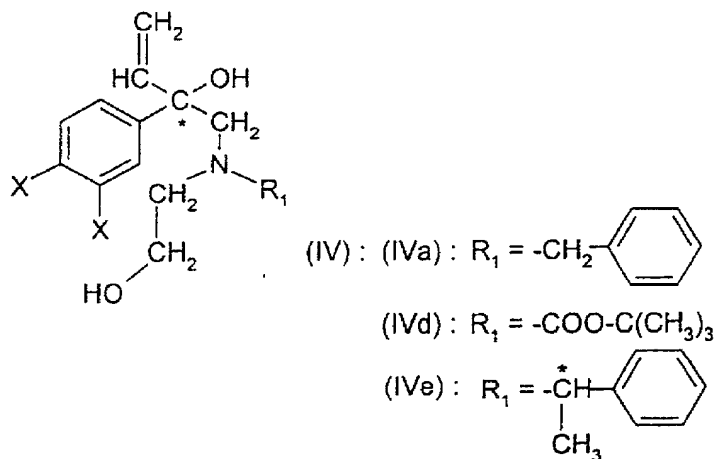


in which X is as defined for a compound of formula (II), with benzyl chloroformate or 1-chloroethyl chloroformate in the presence of a base, with or without solvent.

3. (amended) The process as claimed in claim 1 wherein a compound, in the enantiomerically pure form, in the form of a mixture of diastereoisomers or in the racemic form, of formula:

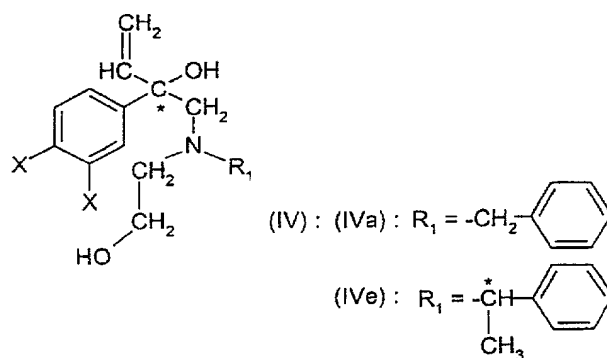


in which X represents a halogen atom and R₁ represents a benzyl group, a *tert*-butyloxycarbonyl group or an α -methylbenzyl group, of its optional salts with inorganic or organic acids, is prepared by cyclization of a compound, in the enantiomerically pure form, in the form of a mixture of diastereoisomers or in the racemic form, of formula:



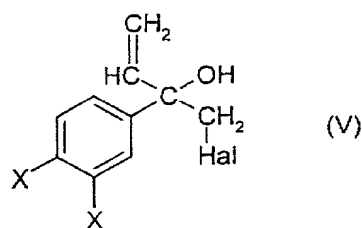
in which X and R₁ are as defined for a compound of formula (II), and, optionally, the compound of formula (II) thus obtained is converted to one of its salts.

4. (amended) The process as claimed in claim 3 wherein a compound, in the enantiomerically pure form, of formula:

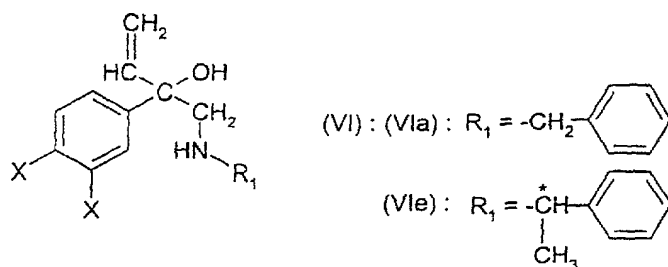


in which X represents a halogen atom and R₁ represents a benzyl group or an α -methylbenzyl group, of its salts with inorganic or organic acids, is prepared:

a) by reaction of a compound, in the racemic form, of formula:



in which X is as defined for a compound of formula (IV) and Hal represents a halogen atom, with benzylamine or with R-(+)- or S-(-)- α -methylbenzylamine in the presence of a base in an inert solvent, to produce a compound, in the racemic form, of formula:



b) by separation of the enantiomers or diastereoisomers of the compound of formula (VI) thus obtained;

c) by reaction of the enantiomerically pure compound of formula (VI) thus obtained:

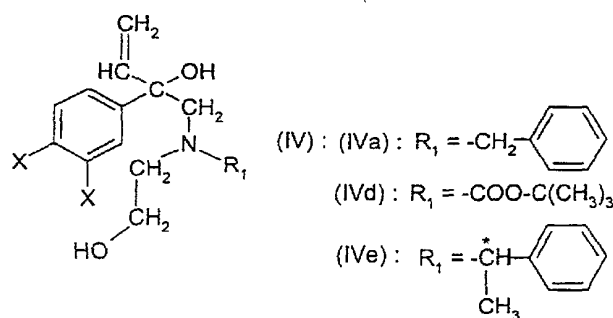
- either with ethylene oxide in the catalytic presence of an acid in an inert solvent;

- or with a compound of formula $Hal'CH_2-CH_2-O-R_2$ (XXI), in which R_2 represents an O-protecting group and Hal' represents a halogen atom, in the presence of a base in an inert solvent, followed by the deprotection of the O-protecting group;

and, optionally, by conversion of the enantiomerically pure compound of formula (IV) thus obtained to one of its salts with inorganic or organic acids.

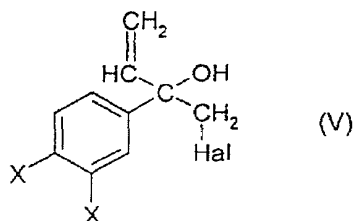
5. (amended) The process as claimed in claim 4 wherein in stage a), use is made of a compound of formula (V) in which Hal represents a chlorine or bromine atom.

6. (amended) The process as claimed in claim 3 wherein a compound, in the racemic form or in the form of a mixture of diastereoisomers, of formula:



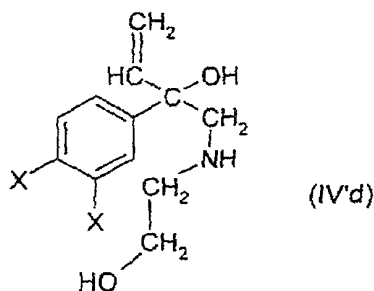
in which X represents a halogen atom and R_1 represents the benzyl group, the *tert*-butyloxycarbonyl group or the α -methylbenzyl group, or one of its optional salts with inorganic or organic acids, is prepared:

- a) by reaction of a compound, in the racemic form, of formula:



in which X is as defined for a compound of formula (IV) and Hal represents a halogen atom, either with 2-(benzylamino)-1-ethanol or with 2-amino-1-ethanol or with (R)- or (S)-2-(α -methylbenzylamino)-1-ethanol, in the presence of a base and in an inert solvent, and, optionally, by conversion of the compound of formula (IVa) or (IVe) thus obtained to one of its salts with inorganic or organic acids;

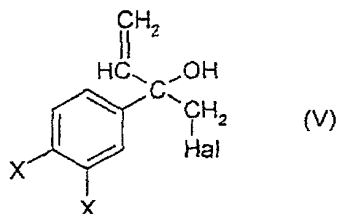
- b) if appropriate, when the compound of formula (V) is employed with 2-amino-1-ethanol in stage a), by reaction of the compound thus obtained, of formula:



with di-*tert*-butyl dicarbonate in the presence of a base and in an inert solvent, to produce the compound of formula (IVd).

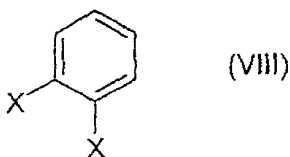
7. (amended) The process as claimed in claim 6 wherein use is made of a compound of formula (V) in which Hal represents a chlorine or bromine atom.

8. (amended) The process as claimed in claim 4 wherein a compound of formula:



in which X represents a halogen atom and Hal represents a halogen atom, is prepared:

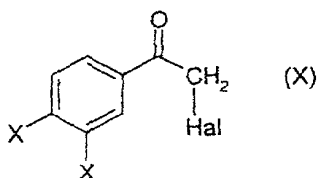
a) by reaction of a compound of formula:



in which X is as defined for a compound of formula (V), with a compound of formula:



in which Hal' and Hal represent a halogen atom, in the presence of a Lewis acid and in an inert solvent, to produce a compound of formula:



b) by reaction of the compound of formula (X) thus obtained with a compound of formula:

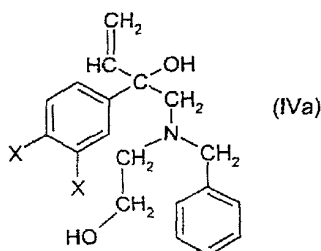


in which Hal'' represents a halogen atom, in an inert solvent, followed by hydrolysis, to produce the compound of formula (V).

9. (amended) The process as claimed in claim 8 wherein a compound of formula (V) in which Hal represents a chlorine or bromine atom is prepared.

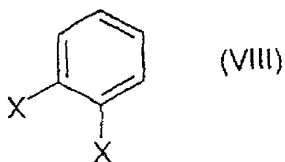
10. (amended) The process as claimed in claim 8 wherein, in stage a), use is made of a compound of formula (IX) in which Hal' and Hal each independently represent a chlorine or bromine atom and, in stage b), use is made of a compound of formula (XI) in which Hal'' represents a chlorine or bromine atom.

11. (amended) The process as claimed in claim 3 wherein a compound, in the racemic form, of formula:



in which X represents a halogen atom, or one of its salts with inorganic or organic acids, is prepared:

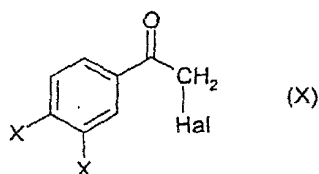
a) by reaction of a compound of formula:



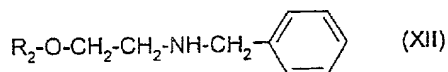
in which X is as defined for a compound of formula (IVa), with a compound of formula:



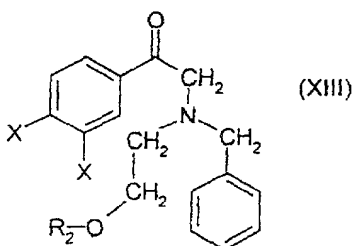
in which Hal' and Hal represent a halogen atom, in the presence of a Lewis acid and in an inert solvent, to produce a compound of formula:



b) by reaction of the compound of formula (X) thus obtained with a compound of formula:



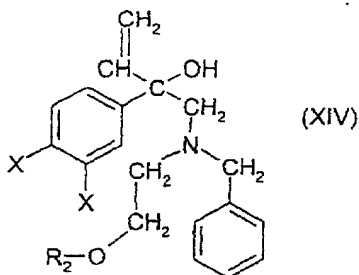
in which R_2 represents an O-protecting group, in the presence of a base and in an inert solvent, to produce a compound of formula:



c) by reaction of the compound of formula (XIII) thus obtained with a compound of formula:



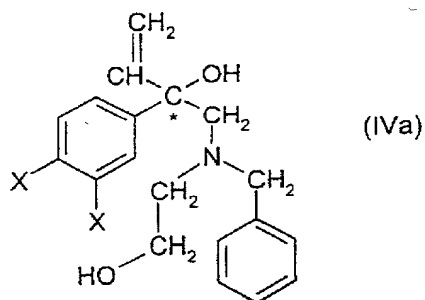
in which Hal'' represents a halogen atom, in an inert solvent, followed by hydrolysis, to produce a compound of formula:



d) by deprotection of the compound of formula (XIV) and, optionally, by conversion of the compound of formula (IVa) thus obtained to one of its salts with inorganic or organic acids.

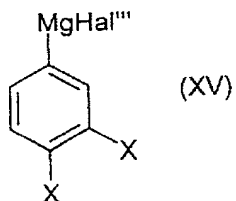
12. (amended) The process as claimed in claim 11 wherein, in stage a), use is made of a compound of formula (IX) in which Hal and Hal' each independently represent a chlorine or bromine atom, in stage b), use is made of a compound of formula (XII) in which R_2 represents a tetrahydropyran-2-yl group, and, in stage c), use is made of a compound of formula (XI) in which Hal'' represents a chlorine or bromine atom.

13. (amended) The process as claimed in claim 3 wherein a compound, in the enantiomerically pure form, of formula:

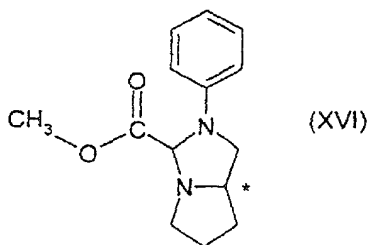


in which X represents a halogen atom, or one of its salts with inorganic or organic acids, is prepared:

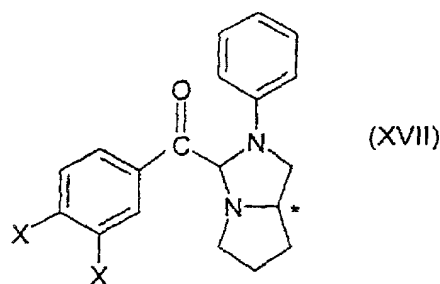
- a) by reaction of a compound of formula:



in which X is as defined for a compound of formula (IVa) and Hal' represents a halogen atom, with methyl (R)- or (S)-2-phenylhexahydropyrrolo[1,2-c]imidazole-3-carboxylate, of formula:



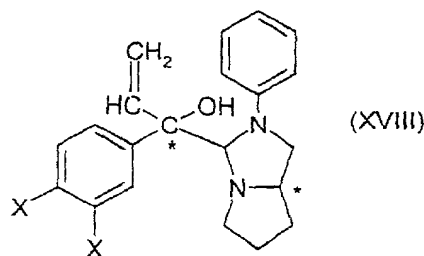
in the presence of magnesium chloride in an inert solvent, followed by hydrolysis, to produce a compound, in the enantiomerically pure form, of formula:



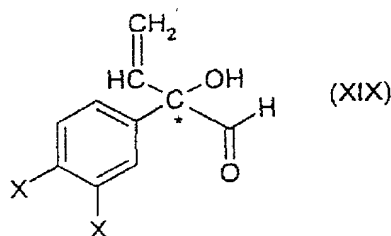
b) by reaction of the compound of formula (XVII) thus obtained with a compound of formula:



in which Hal'' represents a halogen atom, in an inert solvent, followed by hydrolysis, to produce a compound, in the enantiomerically pure form, of formula:

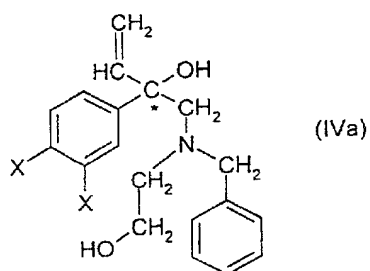


c) by hydrolysis of the compound of formula (XVIII) thus obtained by the action of an acid in an inert solvent as a mixture with water, to produce a compound, in the enantiomerically pure form, of formula:



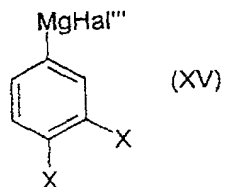
d) by reaction of the compound of formula (XIX) thus obtained with 2-(benzylamino)-1-ethanol in the presence of an acid in an inert solvent, then reduction of the iminium salt formed as an intermediate by means of a reducing agent and, optionally, conversion of the enantiomerically pure compound of formula (IVa) to one of its salts with inorganic or organic acids.

14. (amended) The process as claimed in claim 3 wherein a compound, in the enantiomerically pure form, of formula:

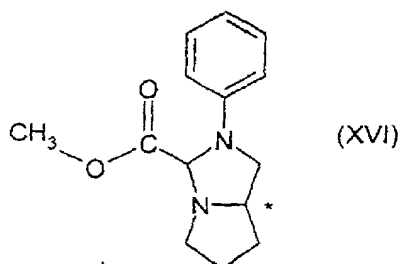


in which X represents a halogen atom, or one of its salts with inorganic or organic acids, is prepared:

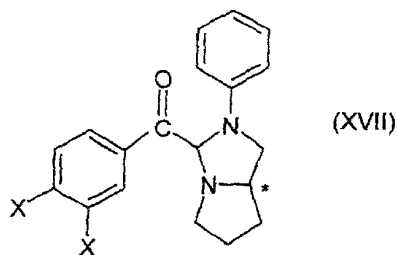
a) by reaction of a compound of formula:



in which X is as defined for a compound of formula (IVa) and Hal' represents a halogen atom, with methyl (R)- or (S)-2-phenylhexahydropyrrolo[1,2-c]imidazole-3-carboxylate, of formula:



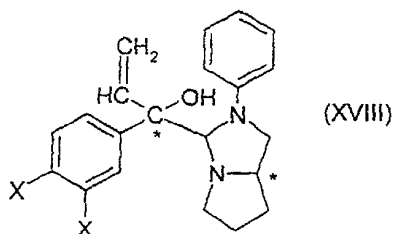
in the presence of magnesium chloride in an inert solvent, followed by hydrolysis, to produce a compound, in the enantiomerically pure form, of formula:



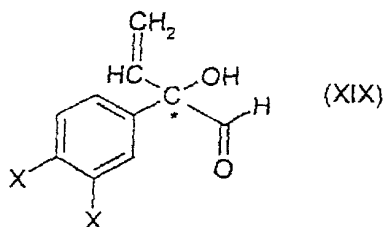
b) by reaction of the compound of formula (XVII) thus obtained with a compound of formula:



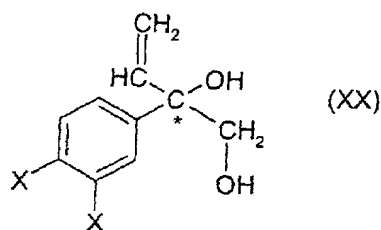
in which Hal'' represents a halogen atom, in an inert solvent, followed by hydrolysis, to produce a compound, in the enantiomerically pure form, of formula:



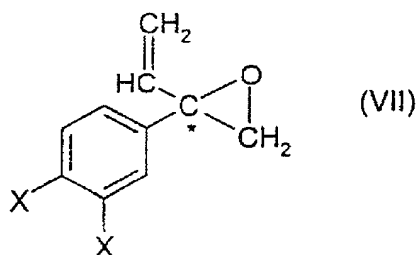
c) by hydrolysis of the compound of formula (XVIII) thus obtained by the action of an acid in an inert solvent as a mixture with water, to produce a compound, in the enantiomerically pure form, of formula:



d) by reduction of the compound of formula (XIX) thus obtained by means of a reducing agent in an inert solvent, to produce a compound of formula:



e) by cyclization of the compound of formula (XX) thus obtained, to produce a compound, in the enantiomerically pure form, of formula:



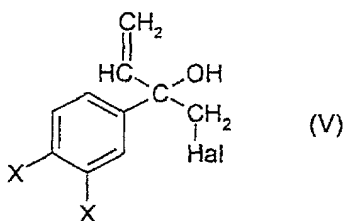
f) by reaction of the compound of formula (VII) thus obtained with 2-(benzylamino)-1-ethanol in the presence of a base and in an inert solvent and, optionally, conversion of the enantiomerically pure compound of formula (IVa) thus obtained to one of its salts with inorganic or organic acids.

15. (amended) The process as claimed in claim 13 wherein, in stage a), use is made of a compound of formula (XV) in which Hal' represents a chlorine or bromine atom and, in stage b), use is made of a compound of formula (XI) in which Hal'' represents a chlorine or bromine atom.

16. The process as claimed in one of claims 1, 2, 3, 4, 6, 8, 11, 13 and 14 wherein compounds of formula (I), (IIa), (IIb), (IIc), (IId), (IIf), (IVa), (IVd), (IVe) or (V) in which X represent a chlorine atom or a fluorine atom are prepared.

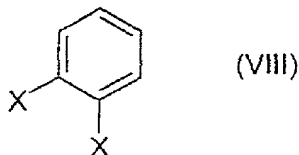
Please add the following new claims:

32. (New) A process according to claim 6 wherein a compound of formula:



in which X represents a halogen atom and Hal represents a halogen atom, is prepared:

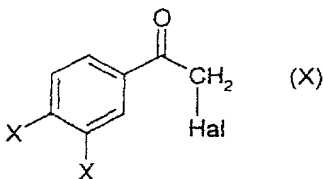
- a) by reaction of a compound of formula:



in which X is as defined for a compound of formula (V), with a compound of formula:



in which Hal' and Hal represent a halogen atom, in the presence of a Lewis acid and in an inert solvent, to produce a compound of formula:



- b) by reaction of the compound of formula (X) thus obtained with a compound of formula:



in which Hal'' represents a halogen atom, in an inert solvent, followed by hydrolysis, to produce the compound of formula (V).

33. (New) The process as claimed in claim 14 wherein in stage a), use is made of a compound of formula (XV) in which Hal' represents a chlorine or bromine atom and, in stage b), use is made of a compound of formula (XI) in which Hal'' represents a chlorine or bromine atom.

34. (New) The process as claimed in claim 32 wherein the compound of formula (V) in which X represents a chlorine atom or a fluorine atom is prepared.

REMARKS

Claims 1-16 have been amended in order to write these claims in the appropriate U.S. claim format.

Claims 8 and 15 have been amended in order to limit the multiple dependencies of these claims.

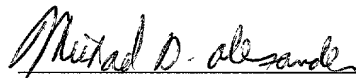
Claims 32-34 have been added by the foregoing amendments. Support for claim 32 occurs, for example, in original claim 8; support for claim 33 occurs, for example, in original claim 15; and support for claim 34 occurs, for example, in original claim 16.

Claims 1-34 remain in the application.

Attached hereto is a marked-up version of the changes made to the specification and claims by the instant amendment. The marked-up version is entitled "Version With Markings To Show Changes Made".

Respectfully submitted,

Date: January 9, 2002


Michael D. Alexander
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 Version With Markings to Show Changes Made 09 JAN 2002

In the specification:

The following Abstract of the disclosure has been provided as a new page 108:

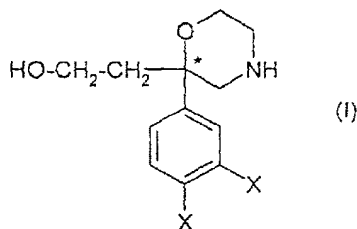
ABSTRACT

The invention relates to a process for the preparation of substituted 2-(2-arylmorpholin-2-yl)ethanol derivatives.

In the Claims:

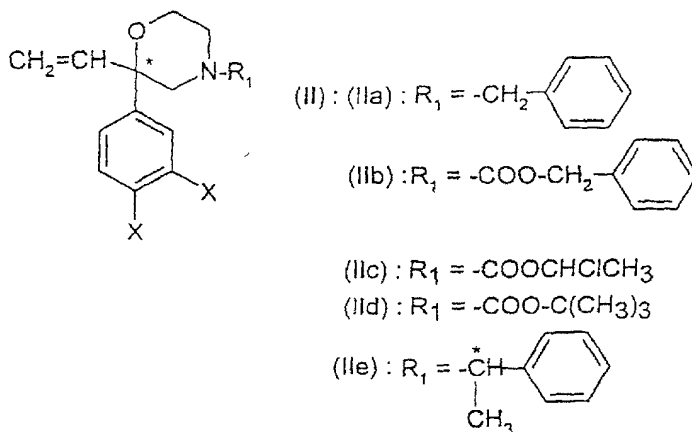
Claims 1-16 have been amended as follows:

1. A process for the preparation of a compound, in the enantiomerically pure form, of formula:



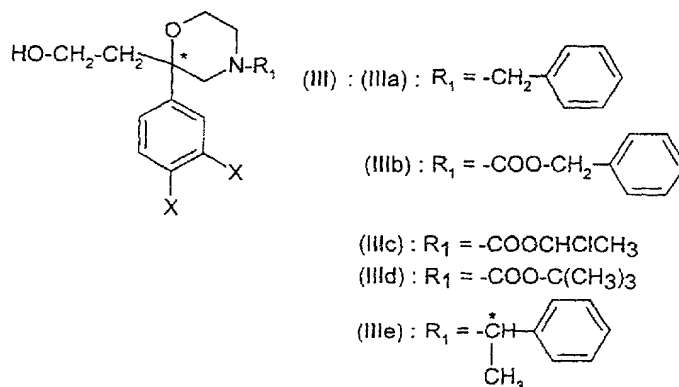
in which X represents a halogen atom, of its salts with inorganic or organic acids or of its salts with optically active organic acids, characterized in that wherein:

- a) a compound, in the racemic form, in the form of a mixture of diastereoisomers or in the enantiomerically pure form, of formula:



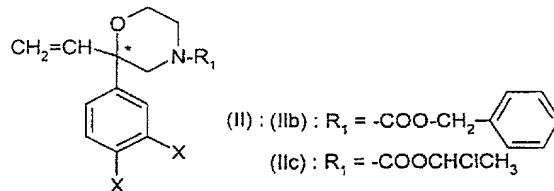
in which X is as defined for a compound of formula (I) and R_1 represents an N-protecting group chosen from a benzyl group, a benzyloxycarbonyl group, a 1-chloroethyloxycarbonyl

group, a *tert*-butoxycarbonyl group or an α -methylbenzyl group, is converted to a compound, in the racemic form, in the form of a mixture of diastereoisomers or in the enantiomerically pure form, of formula:

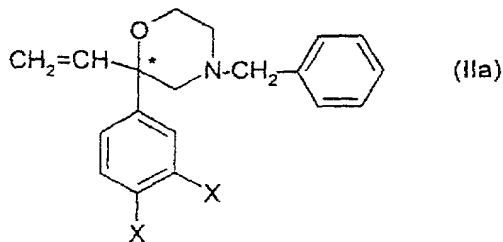


- b) the compound of formula (III) thus obtained is deprotected;
- c) if appropriate, when the compound of formula (I) thus obtained is in the racemic form, the enantiomers are separated, and, optionally, the enantiomerically pure compound of formula (I) is converted to one of its salts with inorganic or organic acids.

2. The process as claimed in claim 1, ~~characterized in that~~ wherein a compound, in the enantiomerically pure form or in the racemic form, of formula:

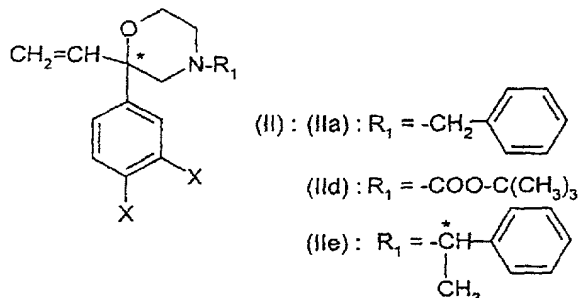


in which X represents a halogen atom and R_1 represents a benzyloxycarbonyl group or a 1-chloroethyloxycarbonyl group, is prepared by reaction of a compound, in the enantiomerically pure form or in the racemic form, of formula:

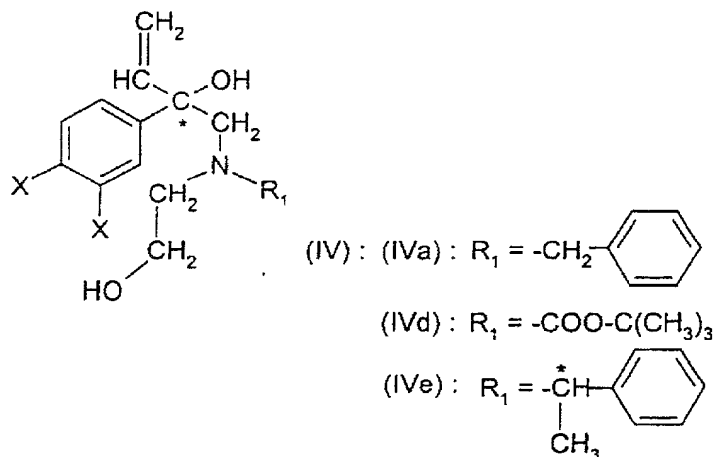


in which X is as defined for a compound of formula (II), with benzyl chloroformate or 1-chloroethyl chloroformate in the presence of a base, with or without solvent.

3. The process as claimed in ~~either of claims claim 1 and 2, characterized in that~~ wherein a compound, in the enantiomerically pure form, in the form of a mixture of diastereoisomers or in the racemic form, of formula:

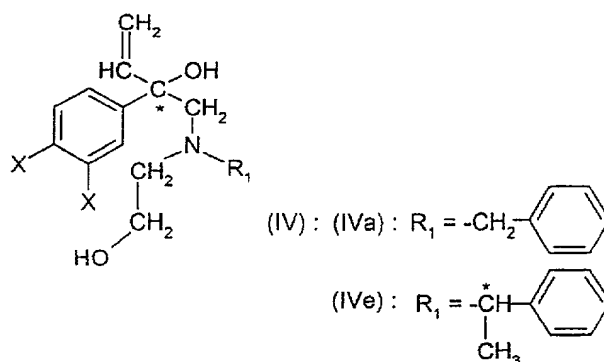


in which X represents a halogen atom and R_1 represents a benzyl group, a *tert*-butyloxycarbonyl group or an α -methylbenzyl group, of its optional salts with inorganic or organic acids, is prepared by cyclization of a compound, in the enantiomerically pure form, in the form of a mixture of diastereoisomers or in the racemic form, of formula:



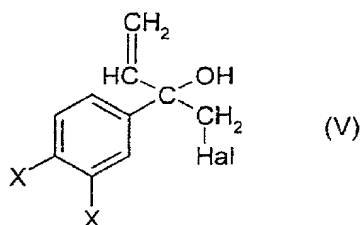
in which X and R_1 are as defined for a compound of formula (II), and, optionally, the compound of formula (II) thus obtained is converted to one of its salts.

4. The process as claimed in claim 3, ~~characterized in that~~ wherein a compound, in the enantiomerically pure form, of formula:

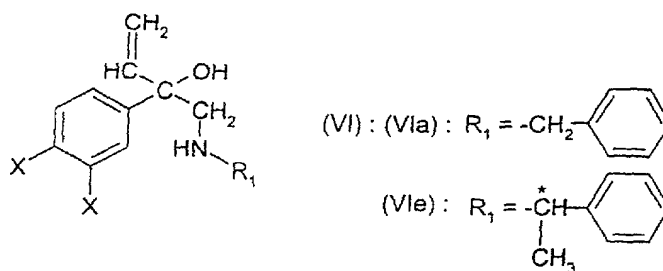


in which X represents a halogen atom and R_1 represents a benzyl group or an α -methylbenzyl group, of its salts with inorganic or organic acids, is prepared:

- a) by reaction of a compound, in the racemic form, of formula:



in which X is as defined for a compound of formula (IV) and Hal represents a halogen atom, with benzylamine or with R-(+)- or S-(-)- α -methylbenzylamine in the presence of a base in an inert solvent, to produce a compound, in the racemic form, of formula:



- b) by separation of the enantiomers or diastereoisomers of the compound of formula (VI) thus obtained;

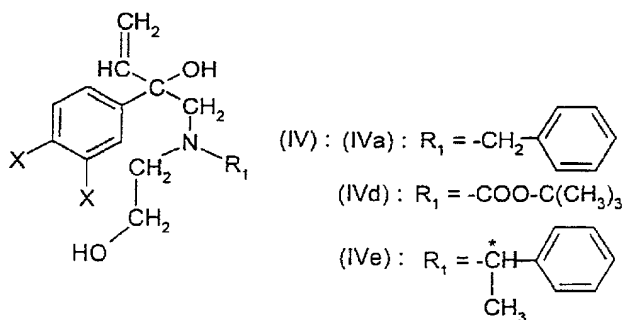
- c) by reaction of the enantiomerically pure compound of formula (VI) thus obtained:

- either with ethylene oxide in the catalytic presence of an acid in an inert solvent;
- or with a compound of formula $Hal^2CH_2-CH_2-O-R_2$ (XXI), in which R_2 represents an O-protecting group and Hal' represents a halogen atom, in the presence of a base in an inert solvent, followed by the deprotection of the O-protecting group;

and, optionally, by conversion of the enantiomerically pure compound of formula (IV) thus obtained to one of its salts with inorganic or organic acids.

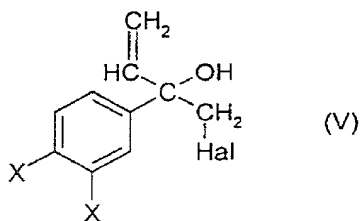
5. The process as claimed in claim 4, ~~characterized in that~~, wherein in stage a), use is made of a compound of formula (V) in which Hal represents a chlorine or bromine atom.

6. The process as claimed in claim 3, ~~characterized in that~~, wherein a compound, in the racemic form or in the form of a mixture of diastereoisomers, of formula:



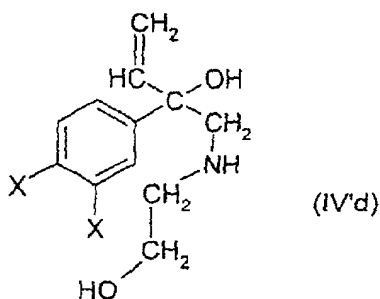
in which X represents a halogen atom and R_1 represents the benzyl group, the *tert*-butyloxycarbonyl group or the α -methylbenzyl group, or one of its optional salts with inorganic or organic acids, is prepared:

a) by reaction of a compound, in the racemic form, of formula:



in which X is as defined for a compound of formula (IV) and Hal represents a halogen atom, either with 2-(benzylamino)-1-ethanol or with 2-amino-1-ethanol or with (R)- or (S)-2-(α -methylbenzylamino)-1-ethanol, in the presence of a base and in an inert solvent, and, optionally, by conversion of the compound of formula (IVa) or (IVe) thus obtained to one of its salts with inorganic or organic acids;

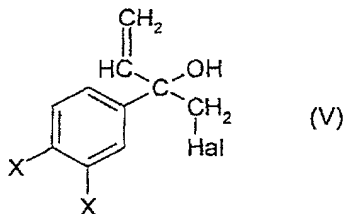
b) if appropriate, when the compound of formula (V) is employed with 2-amino-1-ethanol in stage a), by reaction of the compound thus obtained, of formula:



with di-*tert*-butyl dicarbonate in the presence of a base and in an inert solvent, to produce the compound of formula (IVd).

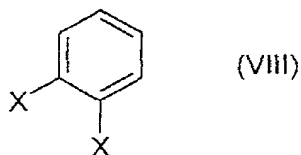
7. The process as claimed in claim 6, ~~characterized in that~~, wherein use is made of a compound of formula (V) in which Hal represents a chlorine or bromine atom.

8. The process as claimed in ~~either of claims claim 4 and 6, characterized in that~~, wherein a compound of formula:



in which X represents a halogen atom and Hal represents a halogen atom, is prepared:

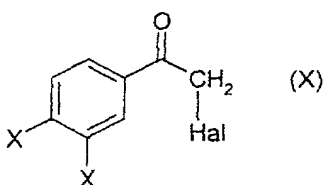
a) by reaction of a compound of formula:



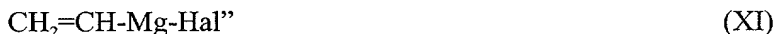
in which X is as defined for a compound of formula (V), with a compound of formula:



in which Hal' and Hal represent a halogen atom, in the presence of a Lewis acid and in an inert solvent, to produce a compound of formula:



b) by reaction of the compound of formula (X) thus obtained with a compound of formula:

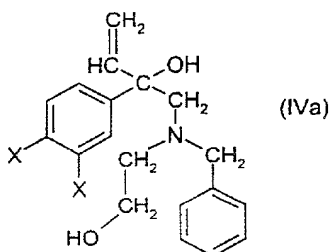


in which Hal'' represents a halogen atom, in an inert solvent, followed by hydrolysis, to produce the compound of formula (V).

9. The process as claimed in claim 8, ~~characterized in that,~~ wherein a compound of formula (V) in which Hal represents a chlorine or bromine atom is prepared.

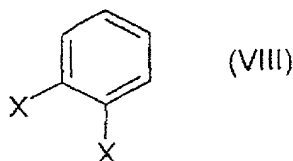
10. The process as claimed in claim 8, ~~characterized in that,~~ wherein, in stage a), use is made of a compound of formula (IX) in which Hal' and Hal each independently represent a chlorine or bromine atom and, in stage b), use is made of a compound of formula (XI) in which Hal'' represents a chlorine or bromine atom.

11. The process as claimed in claim 3, ~~characterized in that,~~ wherein a compound, in the racemic form, of formula:



in which X represents a halogen atom, or one of its salts with inorganic or organic acids, is prepared:

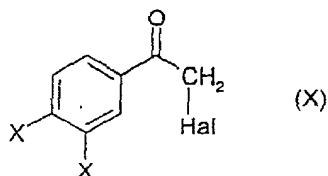
a) by reaction of a compound of formula:



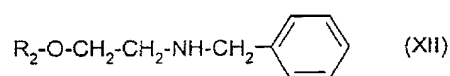
in which X is as defined for a compound of formula (IVa), with a compound of formula:



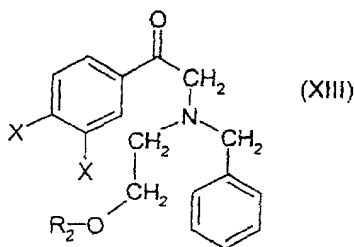
in which Hal' and Hal represent a halogen atom, in the presence of a Lewis acid and in an inert solvent, to produce a compound of formula:



b) by reaction of the compound of formula (X) thus obtained with a compound of formula:



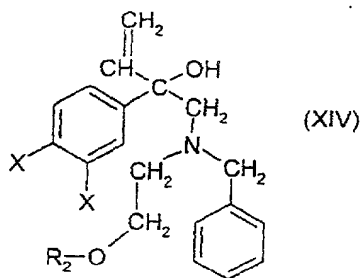
in which R₂ represents an O-protecting group, in the presence of a base and in an inert solvent, to produce a compound of formula:



c) by reaction of the compound of formula (XIII) thus obtained with a compound of formula:



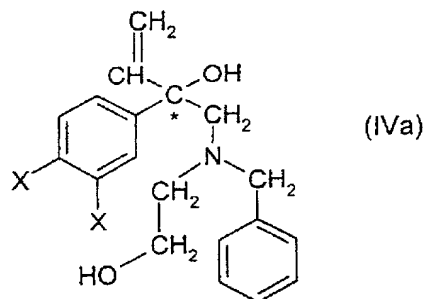
in which Hal'' represents a halogen atom, in an inert solvent, followed by hydrolysis, to produce a compound of formula:



d) by deprotection of the compound of formula (XIV) and, optionally, by conversion of the compound of formula (IVa) thus obtained to one of its salts with inorganic or organic acids.

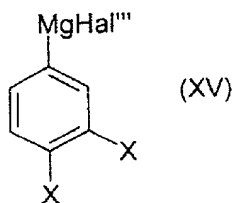
12. The process as claimed in claim 11, ~~characterized in that,~~ wherein, in stage a), use is made of a compound of formula (IX) in which Hal and Hal' each independently represent a chlorine or bromine atom, in stage b), use is made of a compound of formula (XII) in which R₂ represents a tetrahydropyran-2-yl group, and, in stage c), use is made of a compound of formula (XI) in which Hal'' represents a chlorine or bromine atom.

13. The process as claimed in claim 3, ~~characterized in that,~~ wherein a compound, in the enantiomerically pure form, of formula:

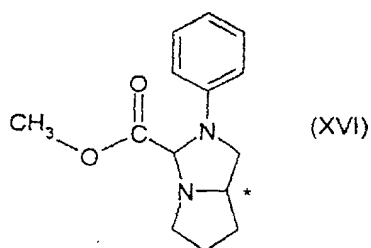


in which X represents a halogen atom, or one of its salts with inorganic or organic acids, is prepared:

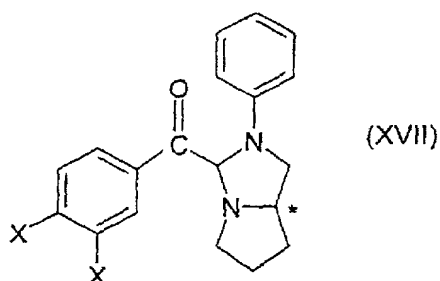
b) by reaction of a compound of formula:



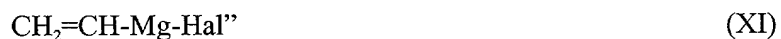
in which X is as defined for a compound of formula (IVa) and Hal' represents a halogen atom, with methyl (R)- or (S)-2-phenylhexahydropyrrolo[1,2-c]imidazole-3-carboxylate, of formula:



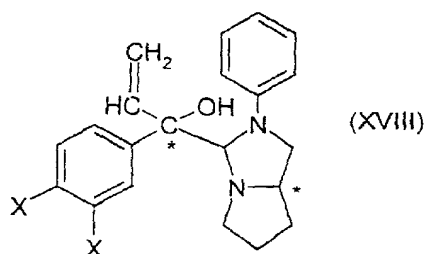
in the presence of magnesium chloride in an inert solvent, followed by hydrolysis, to produce a compound, in the enantiomerically pure form, of formula:



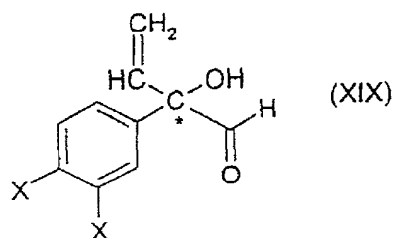
b) by reaction of the compound of formula (XVII) thus obtained with a compound of formula:



in which Hal'' represents a halogen atom, in an inert solvent, followed by hydrolysis, to produce a compound, in the enantiomerically pure form, of formula:

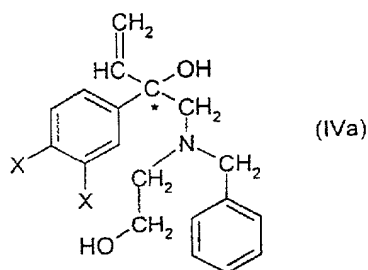


c) by hydrolysis of the compound of formula (XVIII) thus obtained by the action of an acid in an inert solvent as a mixture with water, to produce a compound, in the enantiomerically pure form, of formula:



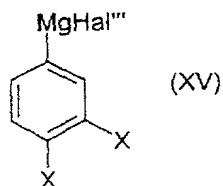
d) by reaction of the compound of formula (XIX) thus obtained with 2-(benzylamino)-1-ethanol in the presence of an acid in an inert solvent, then reduction of the iminium salt formed as an intermediate by means of a reducing agent and, optionally, conversion of the enantiomerically pure compound of formula (IVa) to one of its salts with inorganic or organic acids.

14. The process as claimed in claim 3, ~~characterized in that,~~ wherein a compound, in the enantiomerically pure form, of formula:

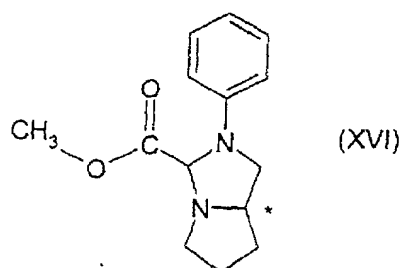


in which X represents a halogen atom, or one of its salts with inorganic or organic acids, is prepared:

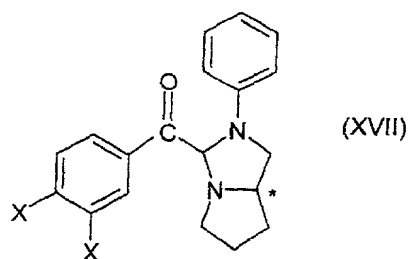
a) by reaction of a compound of formula:



in which X is as defined for a compound of formula (IVa) and Hal' represents a halogen atom, with methyl (R)- or (S)-2-phenylhexahydropyrrolo[1,2-c]imidazole-3-carboxylate, of formula:



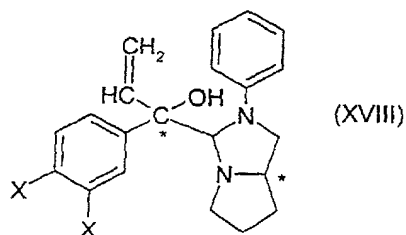
in the presence of magnesium chloride in an inert solvent, followed by hydrolysis, to produce a compound, in the enantiomerically pure form, of formula:



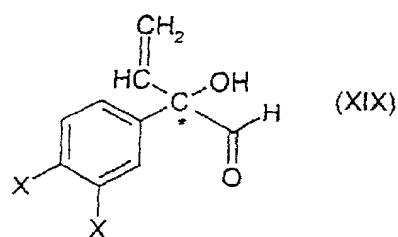
b) by reaction of the compound of formula (XVII) thus obtained with a compound of formula:



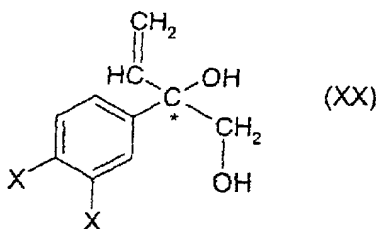
in which Hal'' represents a halogen atom, in an inert solvent, followed by hydrolysis, to produce a compound, in the enantiomerically pure form, of formula:



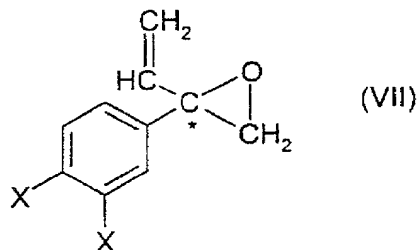
c) by hydrolysis of the compound of formula (XVIII) thus obtained by the action of an acid in an inert solvent as a mixture with water, to produce a compound, in the enantiomerically pure form, of formula:



d) by reduction of the compound of formula (XIX) thus obtained by means of a reducing agent in an inert solvent, to produce a compound of formula:



e) by cyclization of the compound of formula (XX) thus obtained, to produce a compound, in the enantiomerically pure form, of formula:



f) by reaction of the compound of formula (VII) thus obtained with 2-(benzylamino)-1-ethanol in the presence of a base and in an inert solvent and, optionally, conversion of the enantiomerically pure compound of formula (IVa) thus obtained to one of its salts with inorganic or organic acids.

15. The process as claimed in either of claims claim 13 and 14, characterized in that, wherein, in stage a), use is made of a compound of formula (XV) in which Hal' represents a chlorine or bromine atom and, in stage b), use is made of a compound of formula (XI) in which Hal'' represents a chlorine or bromine atom.

16. The process as claimed in one of claims 1, 2, 3, 4, 6, 8, 11, 13 and 14, ~~characterized in that~~ wherein compounds of formula (I), (IIa), (IIb), (IIc), (IId), (IId), (IId), (IVa), (IVd), (IVe) or (V) in which X represent a chlorine atom or a fluorine atom are prepared.

Claims 32-34 have been added.

ABSTRACT

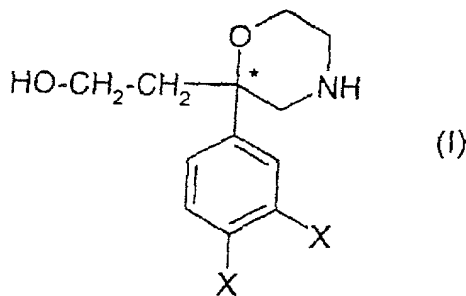
The invention relates to a process for the
5 preparation of substituted 2-(2-arylmorpholin-2-
yl)ethanol derivatives.

PREPARATION OF 2-(2-ARYLMORPHOLIN-2-YL)ETHANOL
DERIVATIVES, AND INTERMEDIATE

A subject matter of the present invention is novel processes for the preparation of substituted
5 2-(2-arylmorpholin-2-yl)ethanol derivatives in the enantiomerically pure form and intermediate compounds of use in these processes.

Substituted 2-(2-arylmorpholin-2-yl)ethanol derivatives of formula:

10



in which X represents a halogen atom and * indicates the position of the asymmetric carbon atom, are key intermediates in the preparation of tachykinin receptor
15 antagonist compounds, such as those disclosed in international application WO 96/23787 and in application EP-A-776 893. Thus, for example, (R)-(+)-3-{1-[2-(4-benzoyl-2-(3,4-difluorophenyl)morpholin-2-yl)ethyl]-4-phenylpiperidin-4-yl}-1,1-dimethylurea is
20 described as a powerful and selective antagonist for human NK₂ receptors of neurokinin A (X. Emonds-Alt et al., Neuropeptides, 1997, 31 (5), 449-458) and, consequently, may be of use in particular in the

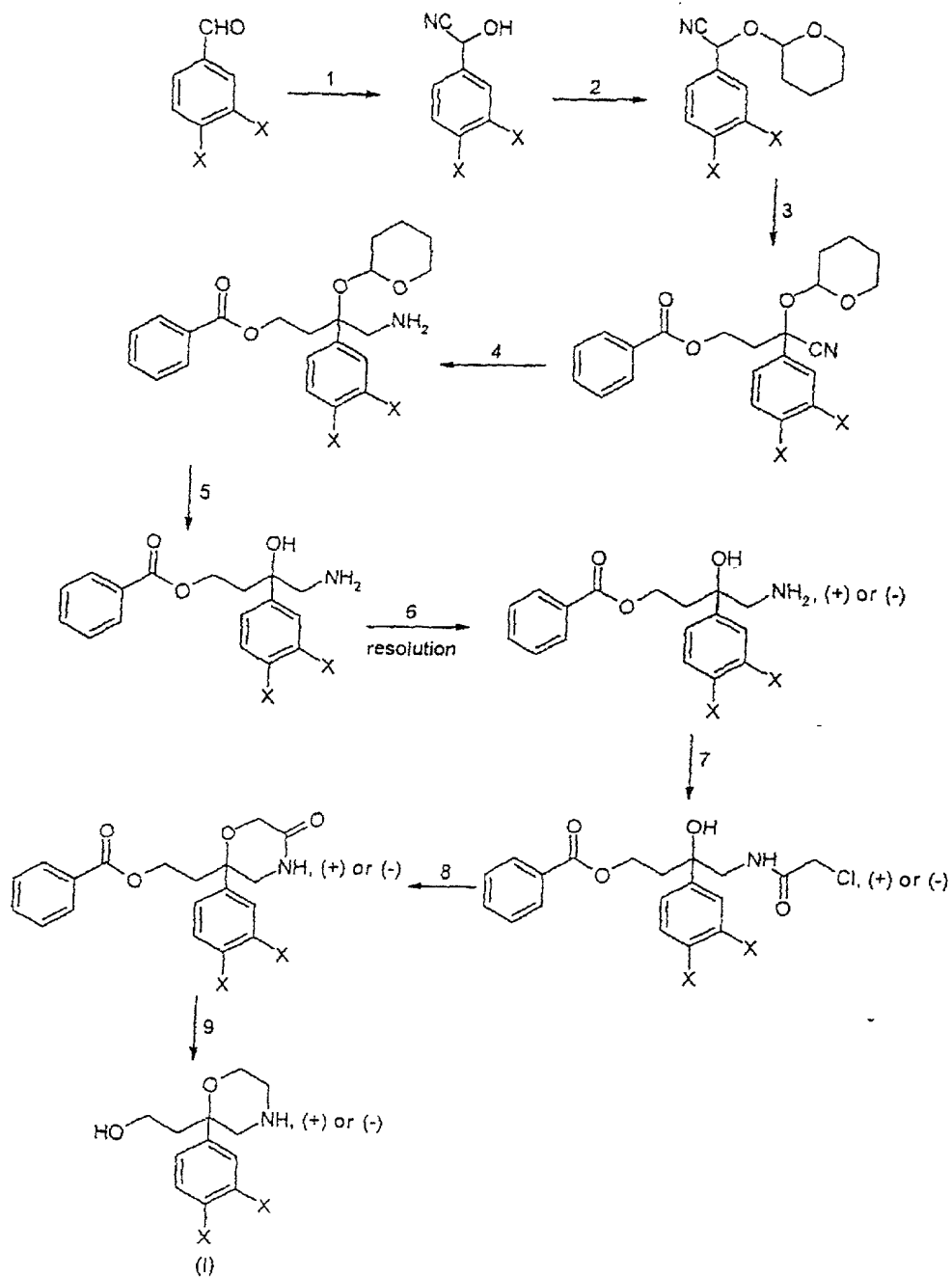
treatment of conditions of the respiratory, gastrointestinal, urinary, immune or cardiovascular system, and of the central nervous system, and of pain and migraine.

- 5 The term "halogen atom" is understood to mean a bromine, chlorine, fluorine or iodine atom.

 Preferably, a subject matter of the present invention is novel processes for the preparation of enantiomerically pure compounds of formula (I) in which
10 X represents a chlorine atom or a fluorine atom.

 The preparation of compounds of formula (I) is illustrated in international application WO 96/23787 and is carried out according to scheme 1 below, in which X represents a halogen atom.

SCHEME 1



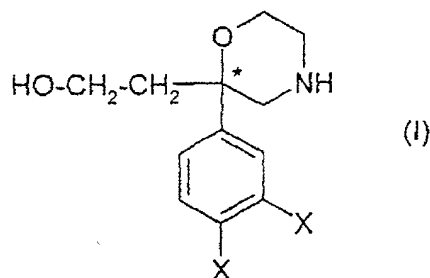
However, this process has disadvantages which are sufficient to exclude it from any use on an industrial scale.

For example, the compound of formula (I) in which X represents a fluorine atom prepared by this process is obtained with a very low yield, of the order of 1 to 2% calculated from the starting benzaldehyde derivative, from the description of application WO 96/23787.

The compound of formula (I) in which X represents a chlorine or fluorine atom can also be prepared according to the enantioselective process described in Tetrahedron: Asymmetry, 1998, 9, 3251-3262. However, this process has the disadvantage of using starting materials, such as diketene, and reagents, such as dichlorobis(triphenylphosphine)-palladium(II), AD-mix- \square [®] or diethyl azodicarboxylate, the costs of which render the production of compound of formula (I) highly expensive on an industrial scale.

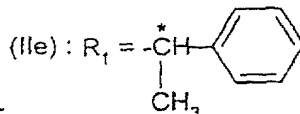
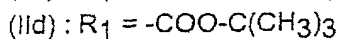
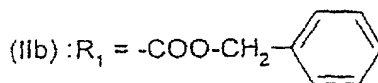
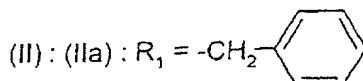
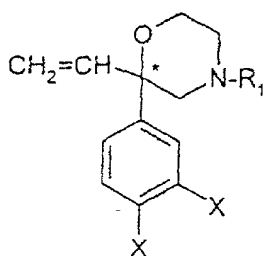
Novel processes for the preparation of the enantiomerically pure compound of formula (I) from simple starting materials and reagents and with yields of the order of 5 to 25% have now been found.

Thus, according to one of its aspects, a subject matter of the present invention is a process A for the preparation of a compound, in the enantiomerically pure form, of formula:

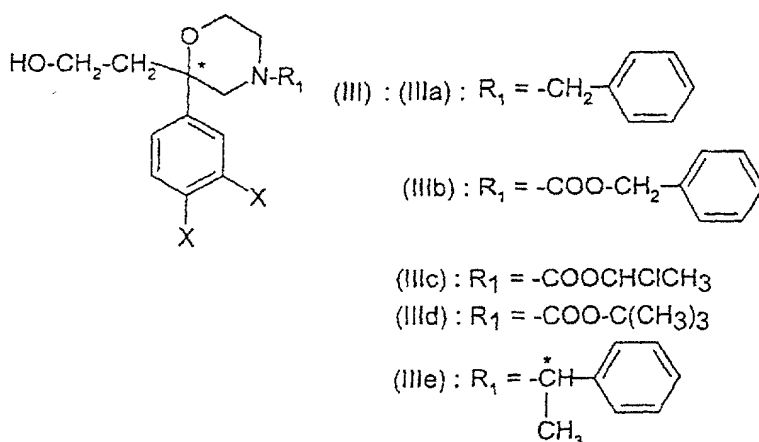


in which X represents a halogen atom, of its salts with inorganic or organic acids or of its salts with optically active organic acids, characterized in that:

- 5 a) a compound, in the racemic form, in the form of a mixture of diastereoisomers or in the enantiomerically pure form, of formula:



- in which X is as defined for a compound of formula (I)
- 10 and R_1 represents an N-protecting group chosen from a benzyl group, a benzyloxycarbonyl group, a 1-chloro-ethyloxycarbonyl group, a *tert*-butyloxycarbonyl group or an α -methylbenzyl group, is converted to a compound, in the racemic form, in the form of a mixture of
- 15 diastereoisomers or in the enantiomerically pure form, of formula:



b) the compound of formula (III) thus obtained is deprotected;

c) if appropriate, when the compound of formula (I) thus obtained is in the racemic form, the enantiomers are separated, and, optionally, the enantiomerically pure compound of formula (I) is converted to one of its salts with inorganic or organic acids.

10 Preferably, in process A, R_1 represents a benzyl group or a benzyloxycarbonyl group.

When X represents a chlorine atom, preferably, in process A, R_1 represents a *tert*-butyloxycarbonyl group or a 1-chloroethyloxycarbonyl group.

15 group.

When, in process A according to the invention, non-racemizing reactions which retain the chirality are used in stages a) and b), an enantiomerically pure compound of formula (I) is prepared directly using, as starting compound, an enantiomerically pure compound of formula (II).

20

In stage a) of process A, a compound of formula (II) is converted to a compound of formula (III) according to conventional methods well known to a person skilled in the art.

5 Preferably, in stage a), the compound of formula (II) is first subjected to a hydroboration reaction and then to an oxidation reaction to obtain a compound of formula (III).

10 The hydroboration reaction of an asymmetric alkene of formula (II) and then the in situ oxidation reaction of the organoborane formed as an intermediate to give the primary alcohol of formula (III) are carried out according to conventional methods, such as those described in J. Am. Chem. Soc., 1974, 96 (25),
15 7765-7770 or in J. Am. Chem. Soc., 1960, 82, 4708-4712.

 The hydroboration agents used, which are well known to a person skilled in the art, are, for example, either borane complexes, such as the borane-tetrahydrofuran complex or the borane-dimethyl sulfide
20 complex, or 9-borabicyclo[3.3.1]nonane or 9-BBN. The borane used can also be generated in situ, according to conventional methods, from, for example, sodium borohydride or lithium borohydride and an acid, such as a Lewis acid.

25 Use is preferably made of the borane-tetrahydrofuran complex, 9-borabicyclo[3.3.1]nonane or

the borane generated in situ by reaction of trimethylsilyl chloride with sodium borohydride.

When the borane-tetrahydrofuran complex is used, the latter participates in the reaction in a proportion of 0.3 to 1.5 molar equivalents per molar equivalent of compound of formula (II).

When 9-borabicyclo[3.3.1]nonane is used, the latter participates in the reaction in a proportion of 1 to 1.5 molar equivalents per molar equivalent of compound of formula (II).

When the borane is generated in situ by reaction of trimethylsilyl chloride with sodium borohydride, these compounds are each used in a proportion of 3 to 5 molar equivalents per molar equivalent of compound of formula (II).

The hydroboration reaction is carried out in an inert solvent, such as an ether, for example diethyl ether, tetrahydrofuran, dioxane, dimethoxyethane or diethylene glycol dimethyl ether, or such as an aromatic hydrocarbon, for example toluene or xylene, at a temperature of between ambient temperature and the reflux temperature of the solvent and for a time of between 5 and 48 hours.

The organoborane formed as an intermediate substance is subsequently subjected to a conventional oxidation reaction. Preferably, the oxidation reaction is carried out under phase transfer catalysis

conditions using a peroxide, in the presence of a strong base and of a phase transfer catalyst in an inert solvent and water.

It is preferable to use hydrogen peroxide as peroxide. Hydrogen peroxide participates in the reaction in a proportion of 3 to 5 molar equivalents per molar equivalent of compound of formula (II).

The base used during the reaction is chosen from an alkali metal hydroxide, such as sodium hydroxide. It participates in the reaction in a proportion of 1 to 2 molar equivalents per molar equivalent of compound of formula (II).

The phase transfer catalyst is chosen from substituted quaternary ammonium salts, such as tetrabutylammonium hydrogensulfate. It participates in the reaction in a proportion of 0.01 to 0.1 molar equivalent per molar equivalent of compound of formula (II).

The oxidation reaction is carried out in one of the solvents abovementioned above for the hydroboration reaction and at a temperature of between 0°C and 60°C.

This oxidation reaction is highly exothermic and requires control of the flow rate for introduction of the peroxide and of the temperature of the reaction medium.

The reaction takes place over a time of between the duration of introduction of the hydrogen peroxide solution and 48 hours.

As the hydrogen peroxide/tetrahydrofuran
5 mixture is regarded as dangerous at the industrial stage, it is preferable to carry out the oxidation reaction in an aromatic solvent, preferably toluene. In this case, an exchange of solvent may be necessary before the oxidation reaction or, preferably, before
10 the hydroboration reaction.

In stage b) of process A, the compound of formula (III) thus obtained is deprotected according to conventional methods.

Thus, the deprotection of the benzyl group of
15 the compound of formula (IIIa), the deprotection of the benzyloxycarbonyl group of the compound of formula (IIIb) or the deprotection of the α -methylbenzyl group of the compound of formula (IIIe) is carried out by hydrogenolysis, preferably by catalytic hydrogenation,
20 or by hydrogen transfer catalysis.

The catalytic hydrogenation is carried out in an inert solvent, such as an alcohol (methanol, ethanol or propan-2-ol, for example), an aromatic hydrocarbon (toluene or xylene, for example) or an ester (ethyl
25 acetate, for example), or in a mixture of these abovementioned solvents, in the presence of a catalyst, such as palladium-on-charcoal or Raney nickel, under a

pressure of between 1 and 10 bar, at a temperature of between 0°C and 100°C and for a time of between 1 and 24 hours.

The hydrogen transfer catalysis is carried out using ammonium formate in the presence of a catalyst, such as palladium-on-charcoal, in an inert solvent, such as an alcohol (methanol or ethanol, for example), at a temperature of between ambient temperature and the reflux temperature of the solvent and for a time of between 2 and 48 hours.

The deprotection of the 1-chloroethyloxycarbonyl group of the compound of formula (IIIc) is carried out by reaction with methanol at a temperature of between ambient temperature and the reflux temperature of the solvent.

The deprotection of the *tert*-butyloxycarbonyl group of the compound of formula (IIId) is carried out by acid hydrolysis by means of hydrochloric acid or trifluoroacetic acid, for example, in an inert solvent, such as an alcohol (methanol or ethanol, for example), an ether (diethyl ether, dioxane or tetrahydrofuran, for example) or a halogenated hydrocarbon (dichloromethane, for example), and at a temperature of between -10°C and the reflux temperature of the solvent.

When the compound of formula (I) is obtained in the racemic form, the enantiomers are separated in

stage c) according to known methods. Preferably, the separation is carried out by preparation of an optically active salt, by the action of an optically active organic acid, such as L-(+)- or D-(-)-mandelic acid, L-(-)- or D-(+)-di-para-toluoyltartaric acid, L-(+)- or D-(-)-tartaric acid, L-(-)- or D-(+)-dibenzoyltartaric acid or (1R)-(-)- or (1S)-(+)-10-camphorsulfonic acid, and then separation of the isomers, for example by crystallization. The desired enantiomer is released from its salt in basic medium.

Preferably, the separation of the enantiomers of the compound of formula (I) is carried out by formation of an optically active salt, by the action of L-(-)- or D-(+)-di-para-toluoyltartaric acid.

The enantiomerically pure compounds of formula (I) in the form of optically active salts with optically active organic acids are novel and form part of the invention.

The enantiomerically pure compounds of formula (I) in the form of optically active salts with optically active organic acids in which X represents a chlorine atom or a fluorine atom are preferred.

The enantiomerically pure compounds of formula (I) in the form of salts with L-(-)- or D-(+)-di-para-toluoyltartaric acid are preferred.

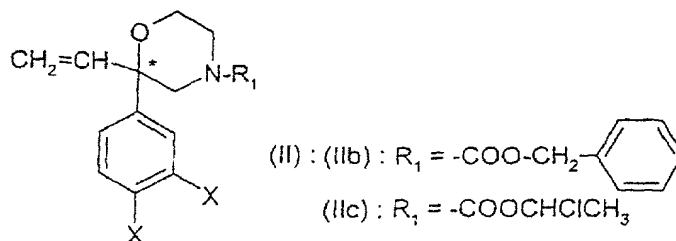
The compounds of formula (II), in the enantiomerically pure form, in the racemic form or in

the form of a mixture of diastereoisomers, and their optional salts with inorganic or organic acids are novel and form part of the invention.

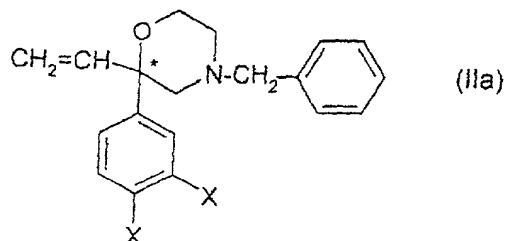
The compounds of formula (II) in which X represents a chlorine atom or a fluorine atom are preferred.

The compounds of formula (II) in which R_1 represents a benzyl group or a benzyloxycarbonyl group are preferred.

According to another of its aspects, a subject matter of the invention is a process B for the preparation of a compound, in the enantiomerically pure form or in the racemic form, of formula:



in which X represents a halogen atom and R_1 represents a benzyloxycarbonyl group or a 1-chloroethyloxycarbonyl group, characterized in that a compound, in the enantiomerically pure form or in the racemic form, of formula:



in which X is as defined for a compound of formula (II), is reacted with benzyl chloroformate or 1-chloroethyl chloroformate in the presence of a base, with or without solvent.

- 5 Preferably, in process B, R_1 represents a benzyloxycarbonyl group.

 The benzyl chloroformate or the 1-chloroethyl chloroformate is used in the reaction in a proportion of 1 to 1.5 molar equivalents per molar equivalent of
10 compound of formula (IIa).

 The base used in the reaction is chosen from organic bases, such as triethylamine, N,N-diisopropylethylamine or N-methylmorpholine, or from alkali metal carbonates or bicarbonates, such as sodium carbonate,
15 potassium carbonate or sodium bicarbonate.

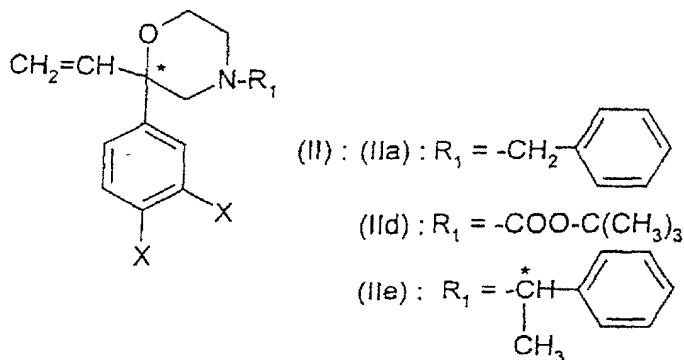
 The base is used in the reaction in a proportion of 0.01 to 1.5 molar equivalents per molar equivalent of compound of formula (IIa).

 When the reaction is carried out in a
20 solvent, the latter is chosen from an aromatic hydrocarbon, such as toluene or xylene, a halogenated hydrocarbon, such as dichloromethane, 1,2-dichloroethane, carbon tetrachloride, chlorobenzene or dichlorobenzene, an ether, such as tetrahydrofuran,
25 dioxane or dimethoxyethane, an ester, such as ethyl acetate, an amide, such as N,N-dimethylformamide, a

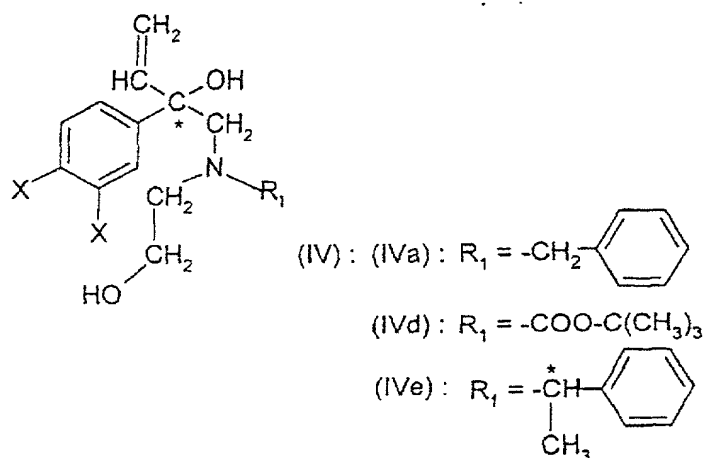
nitrile, such as acetonitrile, or a ketone, such as acetone.

The reaction is carried out at a temperature of between -20°C and the reflux temperature of the solvent and for a time of between 1 to 24 hours.

According to another of its aspects, a subject matter of the invention is a process C for the preparation of a compound, in the enantiomerically pure form, in the form of a mixture of diastereoisomers or in the racemic form, of formula:



in which X represents a halogen atom and R_1 represents a benzyl group, a *tert*-butyloxycarbonyl group or an α -methylbenzyl group, of its optional salts with inorganic or organic acids, characterized in that a compound, in the enantiomerically pure form, in the form of a mixture of diastereoisomers or in the racemic form, of formula:



in which X and R_1 are as defined for a compound of formula (II), is cyclized and, optionally, the compound of formula (II) thus obtained is converted to one of its salts.

Preferably, in process C, R_1 represents a benzyl group.

The reaction for the cyclization of a diol of formula (IV) to a morpholine derivative of formula (II) can be carried out according to known methods as described, for example, in J. Med. Chem., 1994, 37, 2791-2796.

Preferably, the cyclization reaction is carried out under phase transfer catalysis conditions using an alkylsulfonyl or arylsulfonyl halide in the presence of a strong base and of a phase transfer catalyst, in an inert solvent as a mixture with water.

The reaction of the primary alcohol of the compound of formula (IV) with an alkylsulfonyl or arylsulfonyl halide in the presence of a strong base makes it possible first to form an alkylsulfonate or

arylsulfonate ester which, under the reaction conditions, cyclizes in situ to form the morpholine ring.

It has been found that, when the cyclization reaction of an enantiomerically pure compound of formula (IV) is carried out under the abovementioned conditions, an enantiomerically pure compound of formula (II) is obtained, the asymmetric carbon of which has the same configuration.

Preference is given, among alkylsulfonyl or arylsulfonyl halides, to methanesulfonyl chloride, benzenesulfonyl chloride or *p*-toluenesulfonyl chloride.

The alkylsulfonyl or arylsulfonyl halide participates in the reaction in a proportion of 1 to 1.5 molar equivalents per molar equivalent of compound of formula (IV).

The base used during the reaction is chosen from an alkali metal hydroxide, such as sodium hydroxide or potassium hydroxide.

The base participates in the reaction in a proportion of 5 to 10 molar equivalents per molar equivalent of compound of formula (IV).

The phase transfer catalyst is chosen from substituted quaternary ammonium salts, such as benzyltriethylammonium chloride.

The catalyst participates in the reaction in a proportion of 0.01 to 0.1 molar equivalent per molar equivalent of compound of formula (IV).

The reaction is carried out in an inert
5 solvent, such as an aromatic hydrocarbon, for example toluene or xylene.

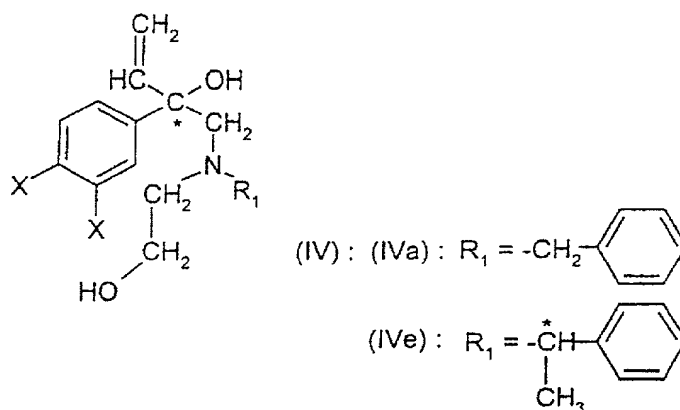
The reaction is carried out at a temperature of between ambient temperature and 60°C and takes place over a period of 1 to 24 hours.

10 The compound of formula (IV), in the enantiomerically pure form, in the form of a mixture of diastereoisomers or in the racemic form, and its optional salts with inorganic or organic acids are novel and form part of the invention.

15 The compound of formula (IV) in which X represents a chlorine atom or a fluorine atom is preferred.

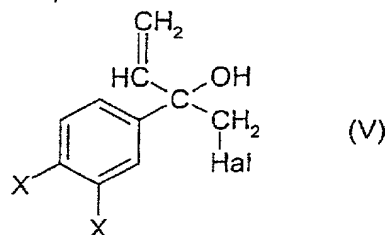
The compound of formula (IV) in which R₁ represents a benzyl group is preferred.

20 According to another of its aspects, a subject matter of the invention is a process D for the preparation of a compound, in the enantiomerically pure form, of formula:



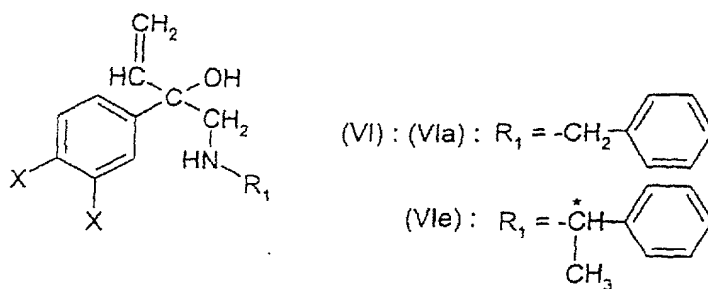
in which X represents a halogen atom and R_1 represents a benzyl group or an α -methylbenzyl group, of its salts with inorganic or organic acids, characterized in that:

- 5 a) a compound, in the racemic form, of formula:



in which X is as defined for a compound of formula (IV) and Hal represents a halogen atom, is reacted with benzylamine or with R-(+)- or S-(-)- α -methylbenzylamine

10 in the presence of a base in an inert solvent, to produce a compound, in the racemic form or in the form of a mixture of diastereomers, of formula:



b) the enantiomers or the diastereoisomers of the compound of formula (VI) thus obtained are separated;

c) the enantiomerically pure compound of formula
5 (VI) is reacted:

- either with ethylene oxide in the catalytic presence of an acid in an inert solvent;

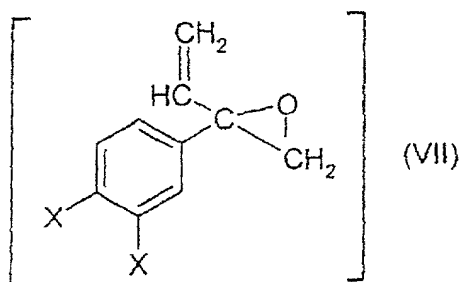
- or with a compound of formula $\text{Hal}'''-\text{CH}_2-\text{CH}_2-\text{O}-\text{R}_2$ (XXI), in which R_2 represents an O-protecting group and
10 Hal''' represents a halogen atom, in the presence of a base in an inert solvent, followed by the deprotection of the O-protecting group;

and, optionally, the enantiomerically pure compound of formula (IV) is converted to one of its
15 salts with inorganic or organic acids.

Preferably, in process D, R_1 represents a benzyl group.

Preferably, in stage a) of process D, use is made of a compound of formula (V) in which Hal
20 represents a chlorine or bromine atom.

In stage a) of process D, the compound of formula (V) is first converted to an intermediate epoxide derivative of formula:



which, under the reaction conditions, reacts with the amine to give the compound of formula (VI).

The amine participates in the reaction in a proportion of 1 to 1.5 molar equivalents per molar equivalent of compound of formula (V).

The base used in the reaction is chosen from alkali metal carbonates or bicarbonates, such as sodium carbonate, potassium carbonate or sodium bicarbonate. Preferably, sodium bicarbonate is used.

The base participates in the reaction in a proportion of 1 to 2 molar equivalents per molar equivalent of compound of formula (V).

The inert solvent is chosen from polar solvents, such as acetonitrile, propionitrile or 1-methyl-2-pyrrolidinone. Propionitrile constitutes a preferred solvent.

The reaction is carried out at a temperature of between 80°C and 120°C.

The reaction is carried out over a period of 5 to 24 hours.

In stage b) of process D, the enantiomers of the compound of formula (VIa) thus obtained are separated according to conventional methods.

Preferably, the separation can be carried out by preparation of an optically active salt by the action of an optically active organic acid, such as L-(+)- or D-(-)-mandelic acid, L-(-)- or D-(+)-di-para-
5 toluoyltartaric acid, L-(+)- or D-(-)-tartaric acid or L-(-)- or D-(+)-dibenzoyltartaric acid, and then separation of the isomers, for example by crystallization. The desired enantiomer is released from its salt in basic medium.

10 Preferably, the separation of the enantiomers of the compound of formula (VIa) is carried out by formation of an optically active salt by the action of L-(+)- or D-(-)-mandelic acid.

 In stage b) of process D, the
15 diastereoisomers of the compound of formula (VIb) thus obtained are separated according to conventional methods. Preferably, the separation can be carried out by preparation of a salt with an inorganic or organic acid or with an optically active organic acid, such as
20 those mentioned above, and then separation of the diastereoisomers, for example by crystallization. The desired diastereoisomer can be released from its salt in basic medium.

 In stage c) of process D, the reaction of the
25 enantiomerically pure compound of formula (VI) with ethylene oxide is carried out in a reactor of

hydrogenator type, since, at the temperatures used, ethylene oxide is in the gaseous form.

The ethylene oxide participates in the reaction in a proportion of 5 to 15 molar equivalents per molar equivalent of compound of formula (VI).

The solvent can, for example, be an alcohol, such as methanol.

The acid used in a catalytic amount in the reaction is chosen from conventional inorganic or organic acids, such as hydrochloric acid or acetic acid.

It has been found that the reaction between the compound of formula (VI) and ethylene oxide can be carried out without acid catalysis by using, as starting compound, the enantiomerically pure compound of formula (VI) in the form of a salt with an optically active acid, preferably with L-(+)- or D-(-)-mandelic acid.

The reaction is carried out at a temperature of between 0°C and 60°C and is carried out for a time of between 2 and 24 hours.

According to the other alternative of stage c) of process D, the protecting group R₂ is chosen from conventional O-protecting group well known to a person skilled in the art, such as the tetrahydropyran-2-yl group.

Use is preferably made of a compound of formula (XXI) in which Hal^{'''} represents a chlorine or bromine atom.

The compound of formula (XXI) participates in the reaction in a proportion of 1 to 2 molar equivalents per molar equivalent of the compound of formula (VI).

The base used in the reaction is chosen from alkali metal carbonates or bicarbonates, such as sodium carbonate, potassium carbonate or sodium bicarbonate.

The base participates in the reaction in a proportion of 1 to 2 molar equivalents per molar equivalent of the compound of formula (VI).

The inert solvent is chosen from polar solvents, such as acetonitrile, propionitrile or 1-methyl-2-pyrrolidone.

The reaction is carried out at a temperature of between 80°C and 120°C and is carried out over a period of 5 to 24 hours.

The deprotection of the O-protecting group R₂ is carried out according to methods known to a person skilled in the art. For example, when R₂ represents a tetrahydropyran-2-yl group, the deprotection is carried out by acid hydrolysis using an acid, such as hydrochloric acid.

The reaction is carried out in an ethereal solvent, such as diethyl ether, or an alcohol, such as

methanol, or in an aromatic solvent, such as toluene, at a temperature of between 0°C and the reflux temperature of the solvent and for a time of between 1 and 24 hours.

5 The compound of formula (VI), in the racemic form, in the form of a mixture of diastereoisomers or in the enantiomerically pure form, and its salts with inorganic or organic acids or its salts with optically active acids are novel and form part of the invention.

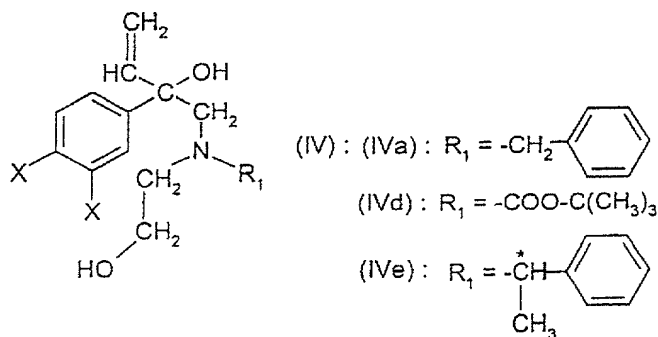
10 The enantiomerically pure compound of formula (VIa) in the form of a salt with L-(+)- or D-(-)-mandelic acid is preferred.

 The compound of formula (VI) in which X represents a chlorine or fluorine atom is preferred.

15 The compound of formula (VI) in which R₁ represents a benzyl group is preferred.

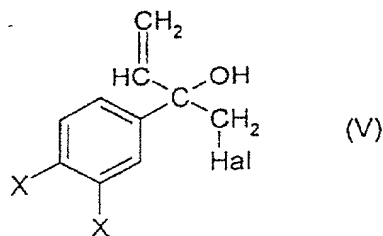
 The compound of formula (XXI) is prepared by protection of 2-haloethanol derivatives according to conventional methods, such as those described in
20 Protective Groups in Organic Chemistry, J.F.W. McOmie, published by Plenum Press, 1973 and in Protective Groups in Organic Synthesis, T.W. Greene and P.G.M. Wutts, published by John Wiley and Sons, 1991.

 According to another of its aspects, a
25 subject matter of the invention is a process E for the preparation of a compound, in the racemic form or in the form of mixture of diastereoisomers, of formula:



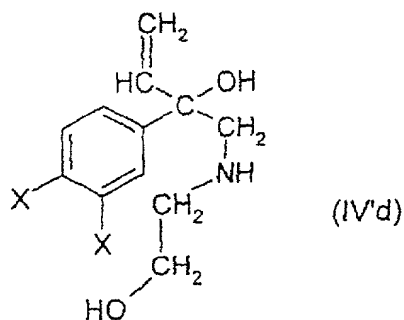
in which X represents a halogen atom and R_1 represents the benzyl group, the tert-butyloxycarbonyl group or the α -methylbenzyl group, of its optional salts with inorganic or organic acids, characterized in that:

a) a compound, in the racemic form, of formula:



in which X is as defined for a compound of formula (IV) and Hal represents a halogen atom, is reacted either with 2-(benzylamino)-1-ethanol or with 2-amino-1-ethanol or with (R)- or (S)-2-(α -methylbenzylamino)-1-ethanol in the presence of a base and in an inert solvent, and, optionally, the compound of formula (IVa) or (IVe) thus obtained is converted to one of its salts with inorganic or organic acids;

b) if appropriate, when the compound of formula (V) is employed with 2-amino-1-ethanol in stage a), the compound thus obtained, of formula:



is treated with di-*tert*-butyl dicarbonate in the presence of a base and in an inert solvent to produce the compound of formula (IVd).

- 5 Preferably, in process E, R_1 represents a benzyl group.

Preferably, in stage a) of process E, use is made of a compound of formula (V) in which Hal represents a chlorine or bromine atom.

- 10 As in stage a) of process D, the compound of formula (V) is first converted to an intermediate epoxide derivative of formula (VII) which, under the reaction conditions, reacts in situ with the aminoethanol derivative to give the compound of formula
- 15 (IVa), (IVe) or (IV'd).

The aminoethanol derivative participates in the reaction in a proportion of 1 to 1.5 molar equivalents per molar equivalent of compound of formula (V).

- 20 The base used in the reaction is chosen from alkali metal carbonates or bicarbonates, such as sodium carbonate, potassium carbonate or sodium bicarbonate. Preferably, sodium bicarbonate is used.

The base participates in a proportion of 1 to 2 molar equivalents per molar equivalent of compounds of formula (V).

The inert solvent is chosen from polar solvents, such as acetonitrile, propionitrile or 1-methyl-2-pyrrolidinone. 1-Methyl-2-pyrrolidinone constitutes a preferred solvent.

The reaction is carried out at a temperature of between 80 and 120°C and for a time of between 10 and 24 hours.

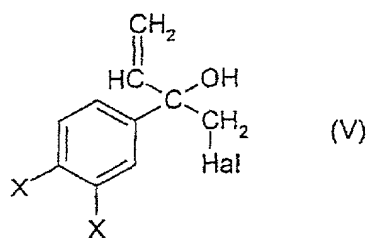
If appropriate, in stage b) of process E, the compound of formula (IV'd) is reacted with di-tert-butyl dicarbonate in the presence of an organic base, such as triethylamine, N,N-diisopropylethylamine or N-methylmorpholine, in an inert solvent, such as dichloromethane, tetrahydrofuran or N,N-dimethylformamide, and at a temperature of between 0°C and 60°C.

(R)- or (S)-2-(α -Methylbenzylamino)-1-ethanol is prepared according to the method described in J. Am. Chem. Soc., 1984, 106, 747-754.

The compounds of formula (V) are novel and form part of the invention.

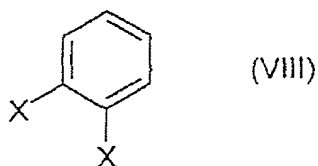
The compound of formula (V) in which X represents a chlorine atom or a fluorine atom and Hal represents a chlorine or bromine atom is preferred.

According to another of its aspects, a subject matter of the invention is a process F for the preparation of a compound of formula:

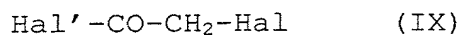


in which X represents a halogen atom and Hal represents a halogen atom, characterized in that:

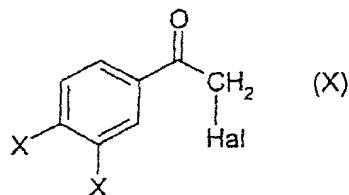
a) a compound of formula:



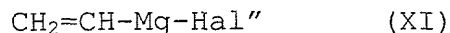
in which X is as defined for a compound of formula (V), is reacted with a compound of formula:



in which Hal' and Hal represent a halogen atom, in the presence of a Lewis acid and in an inert solvent, to produce a compound of formula:



b) the compound of formula (X) thus obtained is reacted with a compound of formula:



in which Hal'' represents a halogen atom, in an inert solvent, followed by hydrolysis, and the expected compound of formula (V) is obtained.

5 According to a preferred aspect, the invention relates to the preparation of a compound of formula (V) in which Hal represents a chlorine or bromine atom.

10 Preferably, in stage a), use is made of a compound of formula (IX) in which Hal' and Hal each independently represent a chlorine or bromine atom and, in stage b), use is made of a compound of formula (XI) in which Hal'' represents a chlorine or bromine atom.

15 Stage a) of process F is a Friedel-Crafts reaction carried out under Perrier conditions according to conventional methods.

The Lewis acid is chosen from conventional Lewis acids; preferably aluminum chloride is used.

20 The Lewis acid is used in the reaction in a proportion of 1 to 1.5 molar equivalents per molar equivalent of compound of formula (VIII).

Preference is given, among haloacetyl halides of formula (IX), to the use of chloroacetyl chloride.

25 The compound of formula (IX) is used in a proportion of 1 to 1.5 molar equivalents per molar equivalent of compound of formula (VIII).

The solvent is chosen from aromatic hydrocarbons, such as toluene or xylene, chlorinated hydrocarbons, such as dichloromethane, dichloroethane, carbon tetrachloride, chlorobenzene or dichlorobenzene, or ethers, such as tetrahydrofuran, dioxane or dimethoxyethane. Preferably, dichloromethane is used.

The reaction is carried out at a temperature of between 0°C and 100°C and for a time of between 1 and 24 hours.

Stage b) of process F is a Grignard reaction carried out according to conventional methods.

The compound of formula (XI) is used in the reaction in a proportion of 1 to 1.5 molar equivalents per molar equivalent of compound of formula (X).

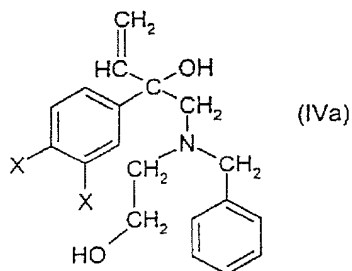
The solvent is chosen from ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran or dioxane. Preferably, tetrahydrofuran is used.

The reaction is carried out at a temperature of between -20°C and 0°C and for a time of between 1 and 24 hours.

At the end of the reaction, the reaction mixture is hydrolyzed according to conventional methods by pouring it, for example, onto a saturated ammonium chloride solution.

According to another of its aspects, a subject matter of the invention is a process G for the

preparation of a compound, in the racemic form, of formula:

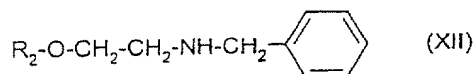


in which X represents a halogen atom, of its salts with inorganic or organic acids, characterized in that:

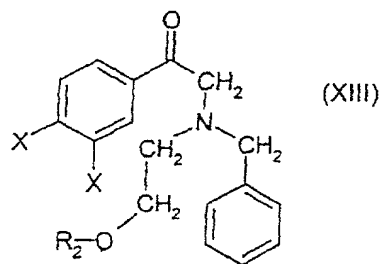
a) the preparation is carried out as in stage a) of process F;

b) the compound of formula (X) thus obtained is reacted with a compound of formula:

10

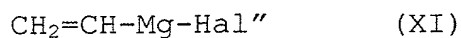


in which R₂ represents an O-protecting group, in the presence of a base and in an inert solvent, to produce a compound of formula:

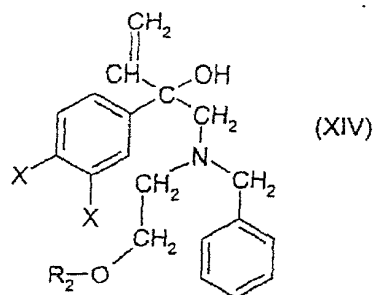


15

c) the compound of formula (XIII) thus obtained is reacted with a compound of formula:



in which Hal" represents a halogen atom, in an inert solvent, followed by hydrolysis, to produce a compound of formula:



- 5 d) the compound of formula (XIV) is deprotected and, optionally, the compound of formula (IVa) thus obtained is converted to one of its salts with inorganic or organic acids.

10 Preferably, in stage a), use is made of a compound of formula (IX) in which Hal' and Hal each independently represent a chlorine or bromine atom.

15 In stage b) of process G, the protecting group R₂ is chosen from conventional O-protecting groups well known to a person skilled in the art, such as the tetrahydropyran-2-yl group.

 The compound of formula (XII) participates in the reaction in a proportion of 1 to 1.5 molar equivalents per molar equivalent of compound of formula (X).

20 The base is chosen from alkali metal carbonates or bicarbonates, preferably sodium bicarbonate.

The base is used in a proportion of 1 to 1.5 molar equivalents per molar equivalent of compound of formula (X).

The inert solvent is chosen from polar solvents, such as acetonitrile or propionitrile, or ethers, such as tetrahydrofuran, or halogenated solvents, such as dichloromethane. Preferably, tetrahydrofuran is used.

The reaction is carried out at a temperature of between ambient temperature and the reflux temperature of the solvent and for a time of between 1 and 24 hours.

Stage c) of process G is a Grignard reaction carried out according to conventional methods.

Preferably, in stage c), use is made of a compound of formula (XI) in which Hal" represents a chlorine or bromine atom.

The compound of formula (XI) is used in the reaction in a proportion of 1.5 to 2 molar equivalents per molar equivalent of compound of formula (XIII).

The solvent is chosen from ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran or dioxane. Preferably, use is made of tetrahydrofuran.

The reaction is carried out at a temperature of between ambient temperature and the reflux temperature of the solvent and takes place for a time of between 1 and 24 hours.

At the end of the reaction, the reaction mixture is hydrolyzed by pouring it, for example, onto a saturated ammonium chloride solution.

The compound of formula (XIV) is deprotected
5 in stage d) of process G according to methods known to a person skilled in the art. For example, when R_2 represents a tetrahydropyran-2-yl group, deprotection is carried out by acid hydrolysis using an acid, such as hydrochloric acid. The latter can be generated in
10 situ from acetyl chloride and methanol.

The reaction is carried out in an ethereal solvent, such as diethyl ether, or an alcohol, such as methanol, at a temperature of between 0°C and the reflux temperature of the solvent and for a time of
15 between 1 and 24 hours.

The compound of formula (XIII) and its salts with inorganic or organic acids are novel and form part of the invention.

The compound of formula (XIII) in which X
20 represents a chlorine or fluorine atom is preferred.

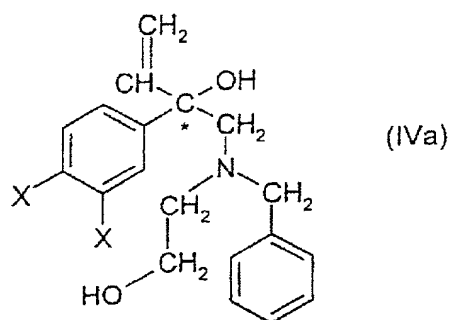
The compound of formula (XIV) and its salts with inorganic or organic acids are novel and form part of the invention.

The compound of formula (XIV) in which X
25 represents a chlorine or fluorine atom is preferred.

The compound of formula (XII) is prepared by protection of the 2-(benzylamino)-1-ethanol according

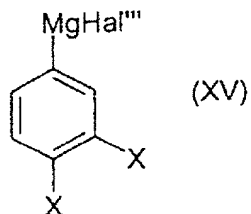
to conventional methods, such as those described in Protective Groups in Organic Chemistry, J.F.W. McOmie, published by Plenum Press, 1973 and in Protective Groups in Organic Synthesis, T.W. Greene and P.G.M. Wutts, published by John Wiley and Sons, 1991.

According to another of its aspects, a subject matter of the invention is an enantioselective process H for the preparation of a compound, in the enantiomerically pure form, of formula:

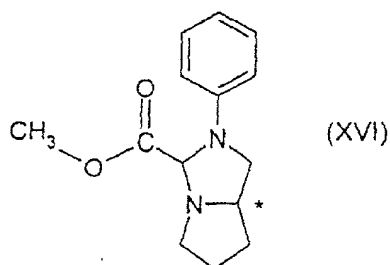


in which X represents a halogen atom, of its salts with inorganic or organic acids, characterized in that:

a) a compound of formula:

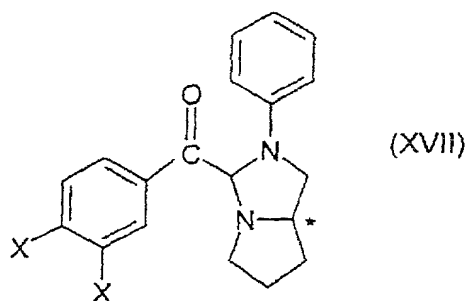


15 in which X is as defined for a compound of formula (IVa) and Hal''' represents a halogen atom, is reacted with methyl (R)- or (S)-2-phenylhexahydropyrrolo-[1,2-c]imidazole-3-carboxylate, of formula:

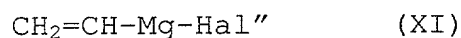


in the presence of magnesium chloride in an inert solvent, followed by hydrolysis, to produce a compound, in the enantiomerically pure form, of formula:

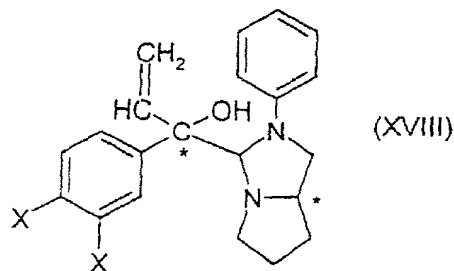
5



b) the compound of formula (XVII) thus obtained is reacted with a compound of formula:

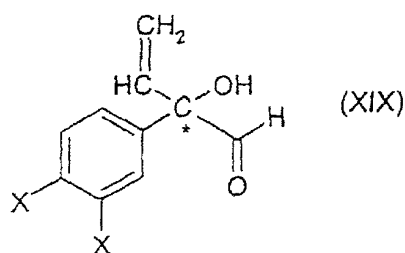


10 in which Hal'' represents a halogen atom, in an inert solvent, followed by hydrolysis, to produce a compound, in the enantiomerically pure form, of formula:



c) the compound of formula (XVIII) thus obtained
15 is hydrolyzed by the action of an acid in an inert

solvent as a mixture with water, to produce a compound, in the enantiomerically pure form, of formula:



- 5 d) the compound of formula (XIX) thus obtained is reacted with 2-(benzylamino)-1-ethanol in the presence of an acid in an inert solvent, then the iminium salt formed as an intermediate is reduced by means of a reducing agent and, optionally, the
- 10 enantiomerically pure compound of formula (IVa) is converted to one of its salts with inorganic or organic acids.

Preferably, in stage a), use is made of a compound of formula (XV) in which Hal''' represents a

15 chlorine or bromine atom and, in stage b), use is made of a compound of formula (XI) in which Hal'' represents a chlorine or bromine atom.

Stages a), b) and c) of process H are carried out according to the method for asymmetric synthesis of

20 α -hydroxyaldehydes described by T. Mukaiyama in Tetrahedron, 1981, 37 (23), 4111-4119.

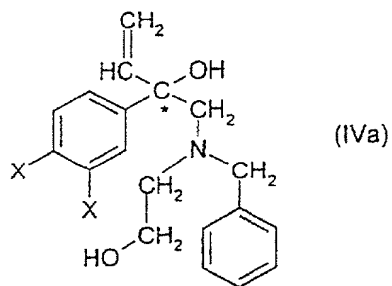
In stage d), an α -hydroxyaldehyde of formula (XIX) is reacted with 2-(benzylamino)-1-ethanol in the presence of an acid, such as acetic acid, in a polar

solvent, such as acetonitrile, to form in situ an intermediate imine which is reduced chemically using, for example, sodium triacetoxyborohydride or sodium cyanoborohydride or catalytically using hydrogen and a catalyst, such as palladium-on-charcoal.

The enantiomerically pure or racemic compound of formula (XIX) is novel and forms part of the invention.

The compound of formula (XIX) in which X represents a chlorine or fluorine atom is preferred.

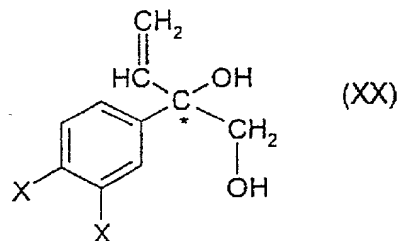
According to another of its aspects, a subject matter of the invention is an enantioselective process I for the preparation of a compound, in the enantiomerically pure form, of formula:



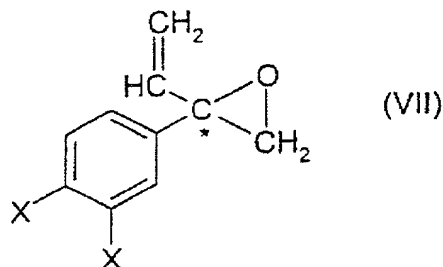
in which X represents a halogen atom, of its salts with inorganic or organic acids, characterized in that:

- a) b) c) the preparation is carried out as in stages
- 20 a), b) and c) of process H;
- d) the compound of formula (XIX) thus obtained is reduced by means of a reducing agent in an inert

solvent to produce an enantiomerically pure compound of formula:



e) the compound of formula (XX) thus obtained is cyclized to produce a compound, in the enantiomerically pure form, of formula:



f) the compound of formula (VII) thus obtained is reacted with 2-(benzylamino)-1-ethanol in the presence of a base and in an inert solvent and, optionally, the enantiomerically pure compound of formula (IVa) is converted to one of its salts with inorganic or organic acids.

In stage d), the reduction of the aldehyde of formula (XIX) to a diol of formula (XX) is carried out according to conventional methods using a reducing agent, such as sodium borohydride, diisobutylaluminum hydride or lithium aluminum hydride. Preferably, sodium borohydride is used.

The reaction is carried out in an inert solvent, such as an aromatic solvent, for example toluene, an alcohol, for example ethanol, an ether, for example tetrahydrofuran, or a mixture of these
5 solvents.

The reaction is carried out at a temperature of between -70°C and the reflux temperature of the solvent and for a time of between 1 and 24 hours.

In stage e), the cyclization of a diol of
10 formula (XX) to an oxirane derivative of formula (VII) is carried out, preferably, under phase transfer catalysis conditions using an alkylsulfonyl or arylsulfonyl halide in the presence of a strong base and of a phase transfer catalyst, in an inert solvent
15 as a mixture with water.

It has been found that, when the cyclization reaction of an enantiomerically pure compound of formula (XX) is carried out under the abovementioned conditions, an enantiomerically pure compound of
20 formula (VII) is obtained, the asymmetric carbon atom of which has the same configuration.

Preference is given, among alkylsulfonyl or arylsulfonyl halides, to methanesulfonyl chloride, benzenesulfonyl chloride or *p*-toluenesulfonyl chloride.

25 The alkylsulfonyl or arylsulfonyl halide participates in the reaction in a proportion of 1 to

1.5 molar equivalents per molar equivalent of compound of formula (XX).

The base used during the reaction is chosen from an alkali metal hydroxide, such as sodium
5 hydroxide or potassium hydroxide.

The base participates in the reaction in a proportion of 5 to 10 molar equivalents per molar equivalent of compound of formula (XX).

The phase transfer catalyst is chosen from
10 substituted quaternary ammonium salts, such as benzyltriethylammonium chloride.

The catalyst participates in the reaction [lacuna] of 0.01 to 0.1 molar equivalent per molar equivalent of compound of formula (XX).

15 The reaction is carried out in an inert solvent, such as an aromatic hydrocarbon, for example toluene or xylene, or a chlorinated solvent, for example dichloromethane.

The reaction is carried out at a temperature
20 of between ambient temperature and 60°C and for a time of between 1 and 24 hours.

In stage f), the opening of the oxirane derivative of formula (VII) by 2-(benzylamino)-1-ethanol is carried out according to conventional
25 methods.

The amine participates in the reaction in a proportion of 1 to 1.5 molar equivalents per molar equivalent of compound of formula (VII).

The base is chosen from alkali metal carbonates or bicarbonates, such as sodium carbonate, potassium carbonate or sodium bicarbonate.

The base participates in the reaction in a proportion of 1 to 2 molar equivalents per molar equivalent of compound of formula (VII).

10 The solvent is chosen from polar solvents, such as acetonitrile, propionitrile or 1-methyl-2-pyrrolidinone.

The reaction is carried out at a temperature of between ambient temperature and 120°C and for a time
15 of between 1 to 48 hours.

It has been found that, when the reaction for opening the enantiomerically pure compound of formula (VII) is carried out under the abovementioned conditions, a compound of formula (IVa) is obtained in
20 which the asymmetric carbon atom has the same configuration.

The enantiomerically pure or racemic compound of formula (XX) is novel and forms part of the invention.

25 The compound of formula (XX) in which X represents a chlorine or fluorine atom is preferred.

The enantiomerically pure or racemic compound of formula (VII) is novel and forms part of the invention.

The compound of formula (VII) in which X
5 represents a chlorine or fluorine atom is preferred.

The compound of formula (XVI) used in stage
a) of process H or in stage a) of process I is prepared
from (S)- or (R)-proline according to the processes
described in Tetrahedron, 1981, 37 (23), 4111-4119, and
10 as illustrated in the examples.

During each of the above processes A to I or
during the various constituent stages of these
processes, the compounds of formula (I), (IIa), (IIb),
(IIc), (IIId), (IIe), (III), (IVa), (IVd), (IVe),
15 (IV'd), (V), (VIa), (VIe), (VIII), (X), (XIII), (XIV),
(XVII), (XVIII), (XIX) and (XX) thus obtained can
subsequently be separated from the reaction medium
according to conventional methods, such as extraction,
crystallization, distillation or chromatography.
20 Furthermore, the various abovementioned compounds
obtained can either be isolated or can be charged
directly to the following process or the following
stage in the medium in which they have been obtained.
Each of the processes A to I or each of the constituent
25 stages of these processes can thus be combined for the
preparation of the compounds of formula (I).

If appropriate, the compounds of formula (I), (IIa), (IIe), (IIIa), (IIIe), (IVa), (IVe), (IV'd), (VIa), (VIe), (XIII) and (XIV) thus obtained can be isolated in the free base or salt form according to conventional techniques.

These salts comprise those with inorganic or organic acids which make possible suitable separation or crystallization of the compounds of formula (I), (IIa), (IIe), (IIIa), (IIIe), (IVa), (IVe), (IV'd), (VIa), (VIe), (XIII) and (XIV), such as the hydrochloride, hydrobromide, sulfate, hydrogensulfate, dihydrogenphosphate, methanesulfonate, methyl sulfate, maleate, fumarate, succinate, naphthalene-2-sulfonate, glyconate, gluconate, citrate, isethionate, benzyne-sulfonate or para-toluenesulfonate.

When the compounds of formula (I), (IIa), (IIe), (IIIa), (IIIe), (IVa), (IVe), (IV'd), (VIa), (VIe), (XIII) and (XIV) are obtained in the free base form, salification is carried out by treatment with the chosen acid in an organic solvent. The corresponding salt is obtained by treatment of the free base, dissolved, for example, in an ether, such as diethyl ether, or in an alcohol, such as methanol, ethanol or propan-2-ol, or in acetone or in dichloromethane or in ethyl acetate, with a solution of the chosen acid in one of the abovementioned solvents, which salt is isolated according to conventional techniques.

Thus, for example, the hydrochloride,
hydrobromide, sulfate, hydrogensulfate,
dihydrogenphosphate, methanesulfonate,
benzynesulfonate, para-toluenesulfonate, oxalate,
5 maleate, succinate, fumarate or naphthalene-2-sulfonate
is prepared.

The compounds of formula (I), (IIa), (IIe),
(IIIa), (IIIe), (IVa), (IVe), (IV'd), (VIa), (VIe),
(XIII) and (XIV) can be isolated in the form of one of
10 their salts, for example the hydrochloride or oxalate;
in this case, if necessary, the free base can be
prepared by neutralization of said salt with an
inorganic or organic base, such as sodium hydroxide or
triethylamine, or with an alkali metal carbonate or
15 bicarbonate, such as sodium carbonate, sodium
bicarbonate, potassium carbonate or potassium
bicarbonate.

According to a preferred aspect, a subject
matter of the invention is processes A to I for the
20 preparation of compound of formula (I), (IIa), (IIb),
(IIc), (IIId), (IIe), (IVa), (IVd), (IVe) and (V) in
which X represents a chlorine atom or a fluorine atom.

According to another preferred aspect, a
subject matter of the invention is compounds of
25 formula (I), in the form of optically active salts with
optically active organic acids, (II), (IV), (V), (VI),

(VII), (XIII), (XIX) and (XX) in which X represents a chlorine atom or a fluorine atom.

Thus, according to the invention, the compounds of formula (I) are prepared by using the
5 above processes A to I and by following the synthetic routes defined below and as illustrated in the examples:

- synthetic route I: process F, stages a and b;
then process E, stage a or stage a and b; then process
10 C; then process A, stages a, b and c.

- synthetic route II: process F, stages a and b;
then process D, stages a, b and c; then process C; then
process A, stages a, b.

- synthetic route III: process G, stages a, b, c
15 and d; then process C; then process A, stages a, b
and c.

- synthetic route IV: process H, stages a, b, c
and d; then process C; then process A, stages a and b.

- synthetic route V: process I, stages a, b, c, d,
20 e and f; then process C; then process A, stages a
and b.

- synthetic routes VI to X: identical to synthetic
routes I to V respectively but carrying out process B
between process C and process A.

25 The following examples illustrate the invention without, however, limiting it.

In the examples below, the following abbreviations are used:

DCM: dichloromethane

THF: tetrahydrofuran

5 AT: ambient temperature.

The proton nuclear magnetic resonance (^1H NMR) spectra are recorded at 200 MHz in d_6 -DMSO using the d_6 -DMSO peak as reference. The chemical shifts δ are expressed in parts per million (ppm). The signals
10 observed are expressed thus: s: singlet; d: doublet; d.d: double doublet; t: triplet; d.t.: double triplet; q: quartet; m: multiplet.

The enantiomeric purities were determined by analysis by High Performance Liquid Chromatography
15 (HPLC) on a Chiracel OD or AD chiral phase (cellulose-based stationary phases) and by supercritical HPLC.

EXAMPLE 1 - Synthetic route I.

(R)-(+)-2-[2-(3,4-Difluorophenyl)morpholin-2-yl]-
1-ethanol, salt with L-(-)-di-para-toluoyltartaric
20 acid.

(I): $\text{X} = \text{F}$

A) 2-Chloro-1-(3,4-difluorophenyl)ethanone.

(X): $\text{X} = \text{F}$; Hal = Cl; process F, stage a).

227.6 g of chloroacetyl chloride (IX: Hal =
25 Hal' = Cl) are added over 10 minutes under a nitrogen atmosphere to a suspension of 247.7 g of aluminum chloride in 450 ml of DCM and then the yellow solution

obtained is heated to reflux. 200 g of

1,2-difluorobenzene (VIII: X = F) are subsequently

added dropwise over 2 hours and then the reaction

mixture is maintained at reflux for 1 hour. After

5 cooling the red-colored reaction mixture to 20°C, the

latter is run onto 1 kg of ice and left stirring for

30 minutes. After separating by settling, the organic

phase is removed, the aqueous phase is extracted with

500 ml of DCM, the combined organic phases are washed

10 with 2 × 500 ml of water, with 500 ml of a saturated

NaHCO₃ solution and with 500 ml of water, the organic

phase is dried over MgSO₄ and the solvent is evaporated

under vacuum. 327.6 g of the expected product are

obtained in the form of a lachrymatory yellow oil.

15 Yield: 97.6%

¹H NMR: δ (ppm): 5.2: s: 2H; 7.6: dd: 1H; 7.8: m:
1H; 8.0: dd: 1H.

B) 1-Chloro-2-(3,4-difluorophenyl)but-3-en-2-ol.

(V) X = F; Hal = Cl; process F, stage b).

20 800 ml of a 1M solution of vinylmagnesium

bromide (XI: Hal" = Br) in THF are cooled to -10°C

under a nitrogen atmosphere, a solution of 152.4 g of

the compound obtained in the preceding stage in 800 ml

of THF is added over 4 hours 30 minutes while

25 maintaining the bulk temperature at -10°C, and then the

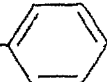
reaction mixture is left stirring for 20 minutes at a

temperature of -10°C. The reaction mixture is

hydrolyzed by running it onto 2 liters of a saturated aqueous ammonium chloride solution and is left stirring for 30 minutes. After separating by settling, the organic phase is washed with 2 x 1 liter of a saturated NaCl solution and then the organic phase is filtered to remove the inorganic salts. 1.5 liters of a solution of the expected compound in THF are obtained, which solution is used directly in the following stage.

^1H NMR: δ (ppm): 3.9: dd: 2H; 5.3: dd: 2H; 5.9: s: 1H; 6.2: m: 1H; 7.3-7.5: m: 3H.

C) 1-[Benzyl(2-hydroxyethyl)amino]-2-(3,4-difluorophenyl)but-3-en-2-ol.

(IVa): $\text{X} = \text{F}$, $\text{R}_1 = -\text{CH}_2-$  ; process E, stage a)

A mixture of 67.2 g of NaHCO_3 and 133 g of 2-(benzylamino)-1-ethanol in 500 ml of 1-methyl-2-pyrrolidinone is heated to 120°C and then the solution of the compound obtained in the preceding stage in THF (1.5 liters) is run in over 3 hours while distilling off the THF from its introduction into the reaction medium. After distilling off 1.5 liters of THF, the reaction mixture is left stirring for 12 hours at 120°C . After cooling to 20°C , the reaction mixture is run onto 2 liters of water, the mixture is extracted with 2 liters of toluene and then the organic phase is washed with 2 x 500 ml of water. 2 liters of water are added to the organic phase, and 75 ml of a concentrated HCl solution are run in. The acidic aqueous phase is

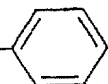
washed with 500 ml of toluene, the aqueous phase is basified by addition of 96 ml of a 10N NaOH solution and extracted with 1.2 liters of toluene, and the organic phase is washed with 500 ml of water. 1.23 kg of toluene solution comprising the expected compound are obtained, which solution is used directly in the following stage.

A dry residue from 50 g of solution comprises 8.9 g of the expected compound, i.e., with respect to the entire solution, 219 g of the expected compound.

Yield: 82%, calculated from the starting compound of stage B of formula (X): $X = F$; $Hal = Cl$.

1H NMR: δ (ppm): 2.5: q: 2H; 2.9: s: 2H; 3.3: q: 2H; 3.6: dd: 2H; 4.5: t: 1H; 5.2: dd: 2H; 5.5: s: 1H; 6.3: dd: 1H; 7.1-7.5: m: 8H.

D) 4-Benzyl-2-(3,4-difluorophenyl)-2-vinylmorpholine maleate.

(IIa) • $C_4H_4O_4$: $X = F$, $R_1 = -CH_2-$  process C.

The toluene solution of the compound obtained in the preceding stage is stirred at 760 rev/min, 7.5 g of benzyltriethylammonium chloride are added and then a freshly prepared and hot solution of 215.5 g of NaOH pellets in 215 ml of water is added, the temperature of the reaction medium rising to 48°C. 139.23 g of benzenesulfonyl chloride are then added dropwise over 2 hours at a flow rate which makes it possible to maintain the bulk temperature at 45°C. After cooling

the reaction mixture to 20°C, it is hydrolyzed by addition of 1 liter of water and left stirring for 1 hour. After separating by settling, the organic phase is washed with 2 × 1 liter of water (pH = 7) and dried
5 over MgSO₄, and the solvent is evaporated under vacuum. 200 g of the expected compound are obtained in the free base form.


Yield: 96.5%.

A suspension of 94.7 g of maleic acid in
10 530 ml of AcOEt is heated at reflux for 10 minutes and then a solution of 257.3 g of the free base compound (IIa: X = F) in 116 ml of AcOEt is added. The reaction mixture is allowed to return to ambient temperature and, at 43°C, crystallization is initiated by addition
15 of 1 g of maleate of the compound (IIa: X = F) to produce rapid precipitation. The reaction mixture is cooled to 0°C and left stirring for 12 hours. The crystallized product is filtered off, washed with 3 × 100 ml of cold AcOEt and dried under vacuum at
20 30°C. 250 g of the expected compound are obtained in the maleate form.

Yield of the salification: 71%.

¹H NMR: δ (ppm): 2.5: m: 2H; 2.9: dd: 2H; 3.7: m: 2H+2H; 5.7: dt: 2H; 5.9: dd: 1H; 6.1: s: 2H; 7.1-7.6:
25 m: 8H.

E) 2-[4-Benzyl-2-(3,4-difluorophenyl)morpholin-2-yl]-1-ethanol hydrochloride.

(IIIa) • HCl:X=F , $\text{R}_1 = -\text{CH}_2-$  process A, stage a).

1 liter of a 0.5M solution of 9-bora-
bicyclo[3.3.1]nonane in THF is introduced into a "pilot
system" reactor (temperature of the oil in the jacket
5 automatically controlled by the bulk temperature)
placed under a nitrogen atmosphere and 500 ml of THF
are distilled off at atmospheric pressure with a bulk
temperature of 74°C. An exchange of solvent at constant
volume is then carried out by introduction of 500 ml of
10 toluene, the exchange lasting 3 hours and the final
temperature being 110°C. The mass is cooled to a
temperature of 20°C and the precipitation of the dimer
of 9-borabicyclo[3.3.1]nonane is observed. A solution
of 131.4 g of the compound obtained in the preceding
15 stage, in the free base form, in 150 ml of toluene is
subsequently added over 25 minutes and the reaction
mixture is left stirring for 12 hours. The reaction
mixture is cooled to 5°C and stirred at 500 rev/min,
and 50 ml of a 10N NaOH solution and then 7 g of
20 tetrabutylammonium hydrogensulfate are added. The bulk
temperature preset value is adjusted to 20°C and 60 g
(53 ml) of an 11M solution of hydrogen peroxide in
water (33%, 130 volumes, $d = 1.13$) are added at a flow
rate by mass of 1 g/min. The bulk preset value is then
25 adjusted to 35°C and 60 g of the 11M hydrogen peroxide
solution are added at a flow rate by mass of 1.5 g/min.
Finally, the bulk preset value is adjusted to 50°C and

60 g of the 11M hydrogen peroxide solution are added at a flow rate by mass of 3 g/min. The mixture is left stirring for 1 hour at a temperature of 50°C. After separating by settling under warm conditions, three phases are observed: toluene/cis-1,5-cyclooctanediol/-water. After removing the aqueous phase, the mixture is cooled to 20°C and the toluene phase is washed with 3 x 200 ml of water to remove the diol. The residual water is removed from the toluene phase by azeotropic entrainment at constant volume with 200 ml of toluene. 1 g of hydrochloride of the expected compound (IIIa: X = F) is then added to the clear toluene phase thus obtained and then 68 ml of a 6.1M solution of HCl in ethanol are added dropwise over 40 minutes. The mixture is cooled to 20°C and left stirring for 3 hours, and the precipitate formed is filtered off, washed with 3 x 100 ml of toluene and dried under vacuum at 30°C. 124.3 g of the expected compound are obtained in the hydrochloride form.

Yield: 80.6%.

¹H NMR: δ (ppm): 2.0: m: 2H; 3.0: m: 2H; 3.2: m: 2H; 3.4: m: 2H; 4.0: dd: 2H; 4.4: s: 2H; 7.1-7.8: m: 8H.

F) 2-[2-(3,4-Difluorophenyl)morpholin-2-yl]-1-ethanol, racemic.

(I): X = F, process A, stage b).

26 g of 50% wet 10% palladium-on-charcoal are introduced into a hydrogenation reactor purged with nitrogen, then a solution of 236.3 g of the compound obtained in the preceding stage in the free base form in 2.6 liters of MeOH is run in and 53 ml of a concentrated HCl solution are added. Hydrogenation is carried out under a pressure of 3 bar at a temperature of 40°C for 1 hour. The reaction mixture is cooled to 20°C and filtered through a Whatman® filter paper, the filter paper is washed with 500 ml of MeOH and the filtrate is concentrated under vacuum to a volume of 500 ml. An exchange of solvent with 500 ml of water is carried out, 80 ml of 10N NaOH are then added to the aqueous solution thus obtained and the mixture is left stirring for 1 hour at 15°C. The precipitate formed is filtered off, washed with 200 ml of water, taken up in 400 ml of diisopropyl ether and left stirring for 1 hour. The precipitate is filtered off, washed with 200 ml of diisopropyl ether and dried under vacuum overnight at 40°C. 120 g of the expected product are obtained.

Yield: 78%.

G) (R)-(+)-2-[2-(3,4-Difluorophenyl)morpholin-2-yl]-1-ethanol, salt with L-(-)-di-para-toluoyltartaric acid.

(I): X = F; process A, stage c).

A suspension of 60 g of the compound obtained in the preceding stage in 780 ml of MeOH is heated to 40°C. It is stirred at 240 rev/min and a solution of 95.3 g of L-(-)-di-para-toluoyltartaric acid in 300 ml of MeOH is added over 50 minutes while maintaining the bulk temperature at 40°C. The reaction mixture is subsequently left stirring for 10 minutes at 40°C and then for 1 hour at 35°C, and is cooled to 20°C over 2 hours 30 minutes. The mixture is left stirring for 12 hours at 20°C and the precipitate formed is filtered off, taken up in 150 ml of MeOH and left stirring for 30 minutes. The precipitate is again filtered off, washed with 60 ml of MeOH and dried under vacuum at 40°C. 64.3 g of the expected compound are obtained in the form of a salt with L-(-)-di-para-toluoyltartaric acid.

Yield: 41.3%.

Final yield: 14.2%, calculated from the starting compound of stage A of formula (VIII): $X = F$.

Enantiomeric purity: 97.5% (e.e. = 95%).

EXAMPLE 2 - Synthetic route II.

(R)-(+)-2-[2-(3,4-Difluorophenyl)morpholin-2-yl]-1-ethanol.

(I): $X = F$.

A) 2-Chloro-1-(3,4-difluorophenyl)ethanone.


(X): $X = F$; Hal = Cl; process F, stage a).

The procedure is identical to that of stage A of example 1.

B) 1-Chloro-2-(3,4-difluorophenyl)but-3-en-2-ol.

(V): X = F; Hal = Cl; process F, stage b).

5 560 ml of a 1.8M solution of vinylmagnesium chloride (XI: Hal'' = Cl) in THF are cooled to -15°C under a nitrogen atmosphere and a solution of 170 g of the compound obtained in the preceding stage in 510 ml of THF is added over 2 hours while maintaining the bulk
10 temperature at -15°C. The reaction mixture is hydrolyzed by running it onto 1 liter of saturated aqueous ammonium chloride solution and is left stirring for 1 hour at ambient temperature. After separating by settling, the organic phase is washed with 2 x 1 liter
15 of a saturated aqueous NaCl solution. 840 ml of a solution of the expected compound in THF are obtained, which solution is used directly in the following stage.
C) 1-(Benzylamino)-2-(3,4-difluorophenyl)but-3-en-2-ol.

(VIa): X = F, R₁ = -CH₂- ; process D, stage a).


A mixture of 81 g of NaHCO₃ and 112.7 g of
20 benzylamine in 190 ml of THF is heated to reflux and 300 ml of the solution of the compound obtained in the preceding stage in THF are quickly added. As soon as reflux is again reached, the THF is distilled off at constant volume while adding the remainder of the
25 preceding solution (540 ml). At the end of the addition, the reaction mixture is concentrated to a THF

volume of 400 ml. An exchange of solvent is then carried out at constant volume with 580 ml of propionitrile, the bulk temperature being 85°C at the end of the exchange. The mixture is left stirring at 85°C for 8 hours. The propionitrile is then removed by solvent exchange at constant volume by addition, over 4 hours 30 minutes, of 1.1 liters of toluene, the bulk temperature being 106°C at the end of the exchange. After cooling to ambient temperature, 1.3 liters of toluene are added to produce 1.9 liters of final solution and then the toluene phase is washed with 2 liters of an aqueous solution comprising 12.5 ml of acetic acid. 1.3 liters of an aqueous solution comprising 80 ml of concentrated HCl are added to the organic phase and the volume is made up by addition of 400 ml of toluene and of the sufficient amount of water to obtain 2.5 liters of aqueous phase, in order to dissolve the oil obtained. After extraction and separation by settling, the organic phase is washed with 500 ml of water and the aqueous phases are combined. The aqueous phases are basified by the addition of 105 ml of 10N NaOH and extracted with 1.3 liters and then with 0.7 liter of diisopropyl ether, the combined organic phases are washed with 3 x 2 liters of water and dried over MgSO₄, and the solvent is evaporated under vacuum. 163 g of the expected product are obtained.

Yield: 64%, calculated from the starting compound of stage B of formula (X): $X = F$; $Hal = Cl$.

1H NMR: δ (ppm): 3.2: dd: 2H; 4.1: s: 2H; 5.2-5.4: dd: 2H; 6.1-6.3: dd: 1H; 7.2-7.6: m: 8H.

- 5 D) R-(+)-1-(Benzylamino)-2-(3,4-difluorophenyl)but-3-en-2-ol, salt with L-(+)-mandelic acid.

(VIa): $X = F$, $R_1 = -CH_2-$  ; process D, stage b).

- A suspension of 36.25 g of L-(+)-mandelic acid in 1.1 liters of diisopropyl ether is heated to 60°C, a solution of 137.9 g of the compound obtained in
- 10 the preceding stage in 555 ml of diisopropyl ether is added over 4 hours and then, at the end of the addition, the reaction medium is heated at 75°C for 1 hour 30 minutes to dissolve the precipitate already formed. The reaction mixture is cooled to 20°C using a
- 15 cooling slope at the rate of 0.3°C/min and is left stirring at 20°C for 8 hours. The precipitate formed is filtered off, resuspended in 600 ml of diisopropyl ether, again filtered off and dried under vacuum at 30°C. 103 g of the expected compound are obtained. The
- 20 compound is taken up in 720 ml of AcOEt and heated to 60°C using a temperature slope at the rate of 1°C/min, and the solution obtained is kept stirred at 60°C for 15 minutes. It is cooled to 0°C with a cooling slope of 1°C/min, crystallization is initiated and the mixture
- 25 is left stirring at 0°C for 4 hours. The precipitate formed is filtered off, washed with 150 ml of


diisopropyl ether and dried under vacuum at 30°C. 60 g of the expected compound are obtained in the form of the salt with L-(+)-mandelic acid.

Yield: 28.5%.

5 Enantiomeric purity: 97.4% (e.e.: 94.8%).

$\alpha_D^{25} = +44.6^\circ$ ($c = 1$, MeOH).

E) (R)-(+)-1-[Benzyl(2-hydroxyethyl)amino]-2-(3,4-difluorophenyl)but-3-en-2-ol.

(IVa): $X = F$, $R_1 = -CH_2-$  ; process D, stage c).

A solution of 70.25 g of the compound

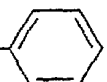
10 obtained in the preceding stage in 200 ml of MeOH is introduced into a Parr reactor, the reactor is placed under vacuum and the solution is cooled to 0°C. Ethylene oxide, preheated to 30°C, is subsequently introduced to a pressure of 1 bar and then the reaction
15 medium is slowly heated to 40°C and left stirring for 4 hours. After having vented off the ethylene oxide and then purged the reaction medium by bubbling with nitrogen, the MeOH is concentrated under vacuum. The residual oil is taken up in 250 ml of water, the
20 aqueous phase is acidified by addition of 13 ml of concentrated HCl, the acidic aqueous phase is washed with 2 × 250 ml of methyl tert-butyl ether, and the aqueous phase is basified by addition of 18 ml of 10N NaOH and extracted with 2 × 250 ml of toluene. The
25 combined organic phases are chromatographed on 500 g of silica, elution being carried out with 5 × 250 ml of a

toluene/AcOEt (50/50; v/v) mixture. The phases are combined and the solvents are concentrated under vacuum. 43.5 g of the expected compound are obtained.

Yield: 81%.

5 $\alpha_D^{25} = +13.9^\circ$ ($c = 1$, MeOH).

F) (R)-(+)-4-Benzyl-2-(3,4-difluorophenyl)-2-vinylmorpholine hydrochloride.

(IIa)·HCl : $X = F$; $R_1 = -CH_2-$  ; process C.

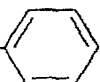
A solution of 40 g of the compound obtained in the preceding stage in 200 ml of toluene is stirred
 10 at 760 rev/min, 1.4 g of benzyltriethylammonium chloride are added and then a freshly prepared and hot solution of 40 g of NaOH pellets in 40 ml of water is added, the temperature of the reaction medium rising to 48°C. 25.43 g of benzenesulfonyl chloride are then
 15 added dropwise over 1 hour at a flow rate which makes it possible to maintain the bulk temperature at 45°C. After cooling the reaction mixture to 20°C, it is hydrolyzed by addition of 200 ml of water and is left stirring for 1 hour. After separating by settling, the
 20 organic phase is washed with 2 × 200 ml of water (pH = 7) and dried over MgSO₄. 20 ml of a 6.1M solution of HCl in ethanol are added dropwise to the toluene solution thus obtained, the mixture is left stirring for 1 hour and the solvents are concentrated under
 25 vacuum. The residue is taken up in 200 ml of toluene and stirred, and the precipitate formed is filtered

off. The precipitate is washed with 100 ml of toluene and is dried under vacuum at 30°C. 37 g of the expected compound are obtained in the hydrochloride form.

Yield: 87%.

5 $\alpha_D^{25} = +19.7^\circ$ (c = 1, MeOH).

G) R-(+)-2-[4-Benzyl-2-(3,4-difluorophenyl)morpholin-2-yl]-1-ethanol hydrochloride.

(IIIa)·HCl: X=F; R₁=-CH₂-; process A, stage a).

- 100 ml of THF are distilled off under vacuum, under a nitrogen atmosphere, from 200 ml of a 0.5M
- 10 solution of 9-borabicyclo[3.3.1]nonane in THF. A solvent exchange at constant volume is then carried out by introduction of 100 ml of toluene and then the solution obtained is cooled to 20°C (precipitation of the dimer of 9-BBN). A solution of 30 g of the compound
- 15 obtained in the preceding stage in the free base form in 35 ml of toluene is added and the mixture is left stirring for 8 hours. 11 ml of a 10N NaOH solution are subsequently added, followed by 1.6 g of tetrabutylammonium hydrogensulfate dissolved in 2 ml of water.
- 20 The reaction mixture is stirred at 500 rev/min and heated to a bulk temperature of 45°C, 31 g of an 11M solution of hydrogen peroxide in water (33%, 130 volumes, d = 1.13) are added over 40 minutes at a flow rate which makes it possible to maintain 45°C in the
- 25 reaction medium, and the reaction medium is left stirring at 45°C for 15 minutes. After separating by

settling, the alkaline aqueous phase is removed, 100 ml of water are added to dissolve the cis-1,5-cyclooctanediol in the form of an oil, and the mixture is stirred and cooled to 20°C. After separating
5 by settling, the organic phase is washed with 2 x 100 ml of water and the residual water is removed from the organic phase by azeotropic entrainment at constant volume until a clear phase is obtained. 16.4 ml of a 6.1M solution of HCl in ethanol are then
10 added dropwise and the mixture is left stirring at 20°C for 1 hour. The precipitate formed is filtered off, washed with 3 x 20 ml of toluene and dried under vacuum at 40°C. 28 g of the expected product are obtained in the hydrochloride form.

15 Yield: 90%.

$$\alpha_D^{25} = +41.6^\circ \quad (c = 1, \text{MeOH}).$$

H) R-(+)-2-[2-(3,4-Difluorophenyl)morpholin-2-yl]-1-ethanol.

(I): X = F; process A, stage b).

20 A solution of 30 g of the compound obtained in the preceding stage in 300 ml of MeOH is added under a nitrogen atmosphere to 3 g of 50% wet 10% palladium-on-charcoal, followed by 30 ml of toluene. Hydrogenation is carried out under a pressure of 1 bar
25 at a temperature of 30°C. The catalyst is filtered off through a Whatman® filter paper, the filter paper is washed with MeOH and then a solvent exchange is carried

out on the filtrate with 120 ml of water. After cooling, the aqueous phase is washed with 2 x 120 ml of methyl *tert*-butyl ether, the aqueous phase is basified by the addition of 9 ml of 10N NaOH and the aqueous phase is left stirring for 1 hour under cold conditions. The precipitate formed is filtered off, washed with 100 ml of diisopropyl ether and dried under vacuum at 40°C. 14 g of the expected product are obtained.

10 Yield: 65%.

Final yield: 7.3%, calculated from the starting compound of stage A of formula (VIII): X = F.

$$\alpha_D^{25} = +21.9^\circ \quad (c = 1, \text{MeOH}).$$

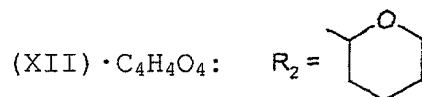
Enantiomeric purity: 99% (e.e. = 98%).

15 EXAMPLE 3 - Synthetic route III.

(R)-(+)-2-[2-(3,4-Difluorophenyl)morpholin-2-yl]-1-ethanol, salt with L-(-)-di-para-toluoyltartaric acid.

(I): X = F.

20 A) N-Benzyl-2-(tetrahydro-2H-pyran-2-yloxy)-1-ethylamine maleate.



100 g of 2-(benzylamino)-1-ethanol are added at ambient temperature to a mixture of 110 g of benzenesulfonic acid in 1.8 liters of DCM, the temperature at the end of the addition being 34.4°C and the pH = 2. The reaction mixture is cooled to 20°C and

105 ml of 3,4-dihydro-2H-pyran are added dropwise, the reaction mixture turning yellow, then pink and finally purple in color at the end of the addition. The mixture is poured onto 2 liters of a 10% aqueous K_2CO_3 solution, then, after separating by settling, the organic phase is dried over Na_2SO_4 and the solvent is evaporated under vacuum. The oil obtained is dissolved in 200 ml of AcOEt, a hot solution of 72.7 g of maleic acid in 655 ml of AcOEt is added and the mixture is left stirring overnight at ambient temperature. The precipitate formed is filtered off, washed with 3×100 ml of AcOEt and dried under vacuum at ambient temperature. 207 g of the expected product are obtained in the maleate form.

Yield: 89%.

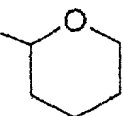
1H NMR: δ (ppm): 1.2-1.7: m: 6H; 3.0: t: 2H; 3.1-3.8: m: 2H; 4.1: s: 2H; 4.5: t: 1H; 7.2-7.4: m: 5H; 8.0: s: 1H.

B) 2-Chloro-1-(3,4-difluorophenyl)ethanone.

(X): X = F; Hal = Cl; process G, stage a).

The procedure is identical to that of stage A of example 1.

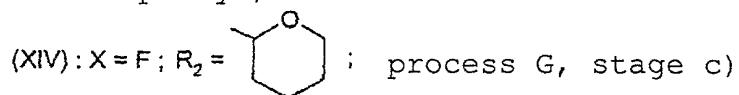
C) 2-{Benzyl[2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-amino}-1-(3,4-difluorophenyl)-1-ethanone.

(XIII): X = F; $R_2 =$  ; process G, stage b).

1.5 liters of a 10% aqueous K_2CO_3 solution are added to a suspension of 200 g of the compound obtained in stage A in 1 liter of DCM and then, after separating by settling, the solvent is evaporated under vacuum and the oil obtained is dissolved in 250 ml of THF. This solution is added to a solution of 52.65 g of $NaHCO_3$ in 10.35ml of water and the reaction mixture is heated to reflux. A solution of 108.55 g of the compound obtained in stage B in 250 ml of THF is then added dropwise over 50 minutes and the mixture is left stirring at reflux for 3 hours. The water is removed by azeotropic entrainment under a nitrogen atmosphere with simultaneous addition of 600 ml of THF over 2 hours. After cooling to ambient temperature, 4 angström molecular sieve is added to the solution and the mixture is left stirring overnight. After filtering under a nitrogen atmosphere, 800 ml of a solution of the expected compound in THF are obtained, which solution is used directly in the following stage.

1H NMR: δ (ppm): 1.4: m: 6H; 2.7: dt: 1H; 3.3: m: 2H; 3.6: m: 2H; 3.7: s: 2H; 4.0: s: 2H; 4.4: m: 2H; 7.0-7.4: m: 8H.

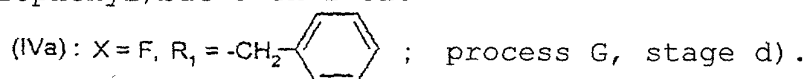
D) 1-{Benzyl[2-(tetrahydropyran-2-yloxy)ethyl]amino}-2-(3,4-difluorophenyl)but-3-en-2-ol.



The solution of the compound obtained in the preceding stage in THF is added over 30 minutes under a

nitrogen atmosphere, at a flow rate which makes it possible to obtain a bulk temperature of 55°C, to 911 ml of a 1M solution of vinylmagnesium bromide (XI: Hal" = Br) in THF and then the reaction mixture is left stirring at 50°C for two hours. The reaction mixture is hydrolyzed by running it onto 1.5 liters of a saturated ammonium chloride solution over 45 minutes while maintaining a bulk temperature of 30°C. 500 ml of water are added. After separating by settling, the aqueous phase is extracted with 1 liter of diisopropyl ether, the organic phases are combined and the solvents are evaporated under vacuum. 241 g of the expected compound are obtained, which is used without further treatment in the following stage.

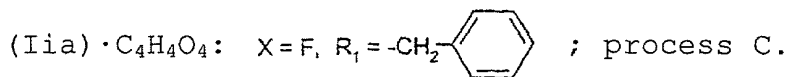
15 E) 1-[Benzyl(2-hydroxyethyl)amino]-2-(3,4-difluorophenyl)but-3-en-2-ol.



500 ml of MeOH are cooled to 5°C and 57 ml of acetyl chloride are added dropwise while maintaining a bulk temperature of 10°C. This solution is then added, over 1 hour at ambient temperature, to a solution of 241 g of the compound obtained in the preceding stage in 500 ml of MeOH and the reaction mixture is left stirring for 2 hours at ambient temperature. The reaction mixture is concentrated under vacuum, the oily residue is dissolved with 1 liter of water, the aqueous phase is washed with 2 × 500 ml of diisopropyl ether,

and the aqueous phase is basified by addition of 40 g of NaOH pellets and extracted with 2 x 800 ml of toluene. 500 ml of water and 400 ml of toluene are added to the organic phase and separation is carried out by settling. 2.083 liters of a solution of the expected compound in toluene are obtained, which solution is used directly in the following stage (content by HPLC: 91 mg/ml, i.e. a mass of 189.5 g of the compound (IVa): X = F)).

F) 4-Benzyl-2-(3,4-difluorophenyl)-2-vinylmorpholine maleate.




6.4 g of benzyltriethylammonium chloride are added to the toluene solution of the compound obtained in the preceding stage and then a freshly prepared and hot solution of 187 g of NaOH pellets in 187 ml of water is added, the bulk temperature being 50°C. 86 ml of benzenesulfonyl chloride are then added dropwise over 2 hours at a flow rate which makes it possible to maintain a bulk temperature of 55°C maximum. After cooling to AT, 1 liter of water is added and the mixture is left stirring for 15 minutes. After separating by settling, the organic phase is washed with 2 x 1 liter of water and with 1 liter of a saturated NaCl solution. The organic phase is chromatographed on 180 g of silica and then the silica is rinsed with 400 ml of toluene. The toluene phases

are combined and the solvent is concentrated under vacuum. 137.8 g of the expected compound are obtained in the free base form.

A suspension of 50.7 g of maleic acid in 284 ml of AcOEt is heated to reflux, then a solution of 137.8 g of the free base compound obtained above in 62 ml of AcOEt is added and the mixture is left stirring for 12 hours while allowing the temperature to return to AT. The mixture is cooled to 0°C and left stirring for 1 hour, and the precipitate formed is filtered off, washed with 4 x 50 ml of cold AcOEt and dried under vacuum at AT. 157 g of the expected compound are obtained in the maleate form.

Yield: 60% calculated from the starting compound of stage C) of formula (X): $X = F$; $Hal = Cl$.

G) 2-[4-Benzyl-2-(3,4-difluorophenyl)morpholin-2-yl]-1-ethanol hydrochloride.

(IIIa)·HCl: $X = F$; $R_1 = -CH_2-$  ; process A, stage a).

500 ml of water are added to a suspension of 245.3 g of the compound obtained in the preceding stage in 500 ml of toluene, and then 120 ml of a 10N sodium hydroxide solution are run in. After separating by settling, the aqueous phase is extracted with 500 ml of toluene, the organic phases are combined and the water is removed by azeotropic entrainment at constant volume with addition of toluene. The toluene solution is concentrated to a volume of 350 ml.

800 ml of a 0.5M solution of 9-borabicyclo-[3.3.1]nonane in THF are introduced into a "pilot system" reactor placed under a nitrogen atmosphere and the solution is concentrated at atmospheric pressure to a volume of 400 ml. 600 ml of the 0.5M solution of 9-BBN in THF are again added and the solution is reconcentrated to a volume of 700 ml of THF. A solvent exchange is then carried out at constant volume by introduction of 700 ml of toluene, the bulk temperature changing from 68°C to 110°C. The mass is cooled to 20°C and precipitation of the dimer of 9-BBN is observed. The 350 ml solution of the compound (IIa): X = F, prepared above is subsequently added and the mixture is left stirring for 8 hours. The reaction mixture is cooled to 5°C and 9.6 g of tetrabutylammonium hydrogensulfate and then 69 ml of 10N NaOH solution are added. The bulk temperature preset value is adjusted to 20°C and 72.3 g of an 11M solution of hydrogen peroxide in water (33%, 130 volumes, d = 1.13) are added at a flow rate by mass of 1.2 g/min. The bulk preset value is then adjusted to 35°C and 72.3 g of the 11M hydrogen peroxide solution are added at a flow rate by mass of 1.8 g/min. Finally, the bulk preset value is adjusted to 50°C and 72.3 g of the 11M hydrogen peroxide solution are added at a flow rate by mass of 3 g/min. The mixture is left stirring for 1 hour at 50°C, separation by settling is carried out under warm

conditions and 3 phases are obtained: toluene/cis-1,5-cyclooctanediol/water. The aqueous phase is removed, the toluene phase is washed with 2 x 200 ml of water to remove the diol, then the organic phase is cooled to 20°C and the organic phase is dried over Na₂SO₄. 95 ml of a 6.1M solution of HCl in ethanol are added to the organic phase, initiation is carried out by addition of 1 g of hydrochloride of the compound (IIIa: X = F) and the mixture is left stirring at AT for 3 hours. The precipitate formed is filtered off, washed with 3 x 250 ml of toluene and dried under vacuum at AT. 164 g of the expected compound are obtained in the hydrochloride form.

Yield: 86%.

H) 2-[2-(3,4-Difluorophenyl)morpholin-2-yl]-1-ethanol, racemic.

(I): X = F; process A, stage b).

16 g of 50% wet 10% palladium-on-charcoal are introduced into a hydrogenation reactor placed under a nitrogen atmosphere and then a solution of 164 g of the compound obtained in the preceding stage in the hydrochloride form in 1.6 liters of NaOH is carefully poured in. The mixture is hydrogenated under a pressure of 3 bar at 40°C for 3 hours. After cooling to AT, the catalyst is filtered off on a Whatman® filter paper, the filter paper is washed with 100 ml of MeOH, 55 ml of 10N NaOH are added to the filtrate and the

MeOH is concentrated under vacuum to a volume of 200 ml. A solvent exchange is carried out with water by azeotropic entrainment. After having removed all the MeOH, the mixture is left stirring for 1 hour and the precipitate formed is filtered off, washed with 2 x 100 ml of water and dried under vacuum overnight at 40°C. 102 g of the expected compound are obtained.

Yield: 94.8%.

I) (R)-(+)-2-[2-(3,4-Difluorophenyl)morpholin-2-yl]-1-ethanol, salt with L-(-)-di-para-toluoyltartaric acid.

(I): X = F; process A, stage c).

A suspension of 95 g of the compound obtained in the preceding stage in 1.235 liters of MeOH is heated to 40°C and a solution of 150.88 g of L-(-)-di-para-toluoyltartaric acid in 475 ml of MeOH is added over 1 hour. When half of this solution has been run in, initiation is carried out by addition of 0.4 g of resolved salt and, when the solution has finished being run in, the mixture is left stirring for 4 hours 30 minutes while allowing the temperature to return to AT. The mixture is cooled to 20°C and stirring continued for 2 hours, and the precipitate formed is filtered off, washed with 2 x 100 ml of EtOH and dried under vacuum at AT. 100 g of the expected compound are obtained in the form of the salt with L-(-)-di-para-toluoyltartaric acid.

Yield: 40.8%.

Final yield: 19.5%, calculated from the starting compound of stage B) of formula (VIII): $X = F$.

Enantiomeric purity: 97.4% (e.e. = 94.8%).

EXAMPLE 4 - Synthetic route IV.

5 (S)-(-)-2-[2-(3,4-Difluorophenyl)morpholin-2-yl]-1-ethanol.

(I): $X = F$.

A) Methyl 2-phenylhexahydro-1*H*-pyrrolo[1,2-*c*]imidazole-3-carboxylate, single isomer (XVI).

10 a) (S)-1-[(Benzyloxy)carbonyl]proline.

This compound is commercially available.

b) Benzyl (S)-2-(anilinocarbonyl)-1-pyrrolidine-carboxylate.

9.7 ml of N-methylmorpholine are added under
15 a nitrogen atmosphere to a solution of 20 g of the compound obtained in the preceding stage in 200 ml of actetonitrile, this solution is then cooled to 0°C and 7.7 ml of ethyl chloroformate are added over 45 minutes. The reaction medium is cooled to 0°C and
20 7.3 ml of aniline are added over 45 minutes. The reaction mixture is concentrated under vacuum, the oily residue is extracted with 200 ml of AcOEt, the organic phase is washed with 2 × 200 ml of a pH = 2 buffer solution, with 200 ml of water and with 2 × 200 ml of a
25 10% aqueous NaHCO₃ solution, 200 ml of ACOEt are added to the organic phase, then the organic phase is dried over Na₂SO₄ and filtered, and the solvent is

concentrated under vacuum. The residue is taken up in 100 ml of *tert*-butyl methyl ether and the mixture is left stirring for 1 hour, and the precipitate formed is filtered off, washed with 20 ml of *tert*-butyl methyl ether and dried under vacuum at 40°C. 20.8 g of the expected product are obtained.

Yield: 80%.

^1H NMR: δ (ppm): 1.8: m: 2H; 2.2: m: 2H; 3.5: m: 2H; 4.3: d.t: 1H; 4.9: d: 1H; 5.1: d: 1H; 7.0-7.4: m: 8H; 8.6: m: 2H; 10: d: 1H.

c) (S)-N-Phenyl-2-pyrrolidinecarboxamide.

A solution of 20 g of the compound obtained in the preceding stage and 5.3 ml of concentrated HCl in 300 ml of MeOH is carefully poured under a nitrogen atmosphere onto 2 g of 50% wet 10% palladium-on-charcoal and hydrogenation is carried out for 2 hours at atmospheric pressure and at AT. 5 ml of concentrated HCl are added, the catalyst is filtered off and the filtrate is concentrated under vacuum. The residue is dissolved in 200 ml of water, the aqueous phase is washed with 200 ml of AcOEt, the aqueous phase is basified by the addition of 5 g of NaOH pellets and extracted with 3 \times 200 ml of DCM. The DCM is removed by azeotropic entrainment with THF and then the THF is evaporated under vacuum. 11.5 g of the expected product are obtained.

Yield: 94.5%.

^1H NMR: δ (ppm): 1.7: m: 2H; 2.0: m: 2H; 2.9: t: 2H; 3.3: s: 1H; 3.7: m: 1H; 7.1: d.d: 1H; 7.3: d.d: 1H; 7.7: d: 2H; 9.9: s: 1H.

d) (S)-N-(2-Pyrrolidinylmethyl)aniline.

5 80 ml of a 1M solution of lithium aluminum hydride in THF are heated to reflux under a nitrogen atmosphere and a solution of 12 g of the compound obtained in the preceding stage in 120 ml of THF is slowly added. The reaction mixture is allowed to return
10 to AT, 3 ml of water, 3 ml of 10N NaOH and 9 ml of water are carefully added, and the mixture is left stirring overnight at AT. The mixture is filtered and the filtrate is concentrated under vacuum. The oil obtained is distilled under vacuum (B.p. =
15 158-164°C/1 mbar). 8.6 g of the expected product are obtained.

Yield: 76%.

^1H NMR: δ (ppm): 1.1: m: 2H; 1.6: m: 2H; 2.6-2.8: m: 4H; 3.1: m: 1H; 5.3: t: 1H; 6.4: m: 3H; 7.0: m: 2H.

20 e) Methyl 2-phenylhexahydro-1H-pyrrolo[1,2-c]-imidazole-3-carboxylate, single isomer.

1.89 g of methyl hydroxymethoxyacetate are added to a solution of 2.64 g of the compound obtained in the preceding stage in 25 ml of toluene and then the
25 mixture is heated at reflux for 1 hour 30 minutes while azeotropically removing the water formed. The reaction mixture is allowed to return to AT, 25 ml of water are

added to dissolve the insoluble materials, the organic phase is dried over MgSO_4 and the solvent is evaporated under vacuum. 3.67 g of the expected product are obtained.

5 Yield: quantitative.

^1H NMR: δ (ppm): 1.4-2.0: m: 4H; 2.6: m: 1H; 3.1: m: 2H; 3.5: m: 1H; 3.6: s: 3H; 3.8: m: 1H; 4.8: s: 1H; 6.4: d.d: 2H; 6.6: dd: 1H; 7.1: dd: 2H.

B) (3,4-Difluorophenyl) (2-phenylhexahydro-1H-
10 pyrrolo[1,2-c]imidazol-3-yl)methanone, single isomer.
(XVII): X = F; process H, stage a).

A solution of 3,4-difluorophenylmagnesium
bromide (XV: X = F; $\text{Hal}''' = \text{Br}$) is prepared from 0.85 g
of magnesium turnings, 4 g of 1-bromo-3,4-
15 difluorobenzene and 20 ml of THF and this solution is
stored at AT..

Furthermore, 0.13 ml of 1,2-dichloroethane is
added under a nitrogen atmosphere to a mixture of 0.4 g
of magnesium turnings in 20 ml of THF and the mixture
20 is heated until it becomes cloudy and gaseous ethylene
is given off. 1.17 ml of 1,2-dichloroethane are then
added in portions of 0.13 ml and the mixture is heated
at reflux for 1 hour. This suspension of anhydrous MgCl_2
thus obtained is allowed to return to AT, a solution of
25 3.67 g of the compound obtained in stage A) in 37 ml of
THF is added, and the mixture is heated at reflux for
1 hour and is allowed to return to AT. This solution is

then cooled to -70°C , 20.4 ml of the solution of 3,4-difluorophenylmagnesium bromide prepared above are added while maintaining a bulk temperature of -70°C , and the mixture is left stirring at -70°C for 1 hour.

- 5 The reaction mixture is poured onto 30 ml of a saturated NH_4Cl solution and is left stirring for 15 minutes. The THF is concentrated under vacuum, the residue is taken up in 50 ml of diisopropyl ether, the organic phase is washed with 30 ml of water and with
10 30 ml of a saturated NaCl solution and dried over MgSO_4 , and the solvent is concentrated under vacuum. 4.59 g of the expected product are obtained.

Yield: 85%.

- C) 1-(3,4-Difluorophenyl)-1-(2-phenylhexahydro-1H-pyrrolo[1,2-c]imidazol-3-yl)-2-propen-1-ol, single
15 isomer.

(XVIII): X = F; process H, stage b).

- A solution of 4.59 g of the compound obtained in the preceding stage in 30 ml of THF is cooled to
20 -70°C , 28 ml of a 1M solution of vinylmagnesium bromide (XI: Hal" = Br) in THF are slowly added while maintaining a bulk temperature of -70°C , and the mixture is left stirring at -70°C for 1 hour. The reaction mixture is poured onto 30 ml of a saturated
25 NH_4Cl solution, the phases are separated by settling and the solvent of the organic phase is concentrated under vacuum. The residue is extracted with 70 ml of diethyl

ether, the organic phase is washed with 30 ml of water and this organic phase is used directly in the following stage.

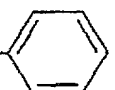
D) 2-(3,4-Difluorophenyl)-2-hydroxybut-3-enal, single
5 isomer.

(XIX): X = F; process H, stage c).

The ethereal solution obtained in the preceding stage is cooled to 5°C, 174 ml of 2% HCl are added and the mixture is left stirring overnight at
10 5°C. The organic phase is washed with 30 ml of water and dried over MgSO₄, and the solvent is concentrated under vacuum. 2.67 g of the expected product are obtained.

Yield: 96% (calculated from the starting compound
15 of stage C of formula (XVII): X = F.

E) (S)-(-)-1-[Benzyl(2-hydroxyethyl)amino]-2-(3,4-difluorophenyl)but-3-en-2-ol.

(IVa): X = F, R₁ = -CH₂-; process H, stage d).


1.2 ml of 2-(benzylamino)-1-ethanol are added to a solution of 1.7 g of the compound obtained in the
20 preceding stage in 34 ml of acetonitrile, followed by 3.63 g of sodium triacetoxymethylborohydride and 3 drops of acetic acid, and the mixture is left stirring for 1 hour at AT. The reaction mixture is hydrolyzed by addition of 50 ml of 1.2M HCl, the organic phase is
25 concentrated under vacuum, the aqueous phase is washed with 50 ml of diisopropyl ether, the aqueous phase is

basified by addition of 7 ml of 10N NaOH and extracted with 50 ml of diisopropyl ether, the organic phase is washed with 2 x 50 ml of water and dried over MgSO₄, and the solvent is evaporated under vacuum. 1 g of the
 5 expected product is obtained.

Yield: 35%.

Enantiomeric purity: 99.4% (e.e. = 98.8%).

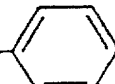
F) (S)-(-)-4-Benzyl-2-(3,4-difluorophenyl)-2-vinyl-morpholine.

(IIa): X = F, R₁ = -CH₂- ; process C.

10 0.04 g of benzyltriethylammonium chloride is added to a solution of 1.2 g of the compound obtained in the preceding stage in 12 ml of toluene and then a freshly prepared and hot solution of 2.34 g of NaOH pellets in 2.4 ml of water is added, the temperature of
 15 the medium rising to 45°C. 0.55 ml of benzenesulfonyl chloride is then added while maintaining the temperature at 50°C. After cooling to AT, 10 ml of water are added and the mixture is left stirring for 1 hour. After separating by settling, the organic phase
 20 is washed with 2 x 50 ml of water and dried over Na₂SO₄, and the solvent is evaporated under vacuum. The residue is chromatographed on 60 g of silica, elution being carried out with the cyclohexane/diethyl ether (90/10, v/v) mixture. 0.8 g of the expected product is
 25 obtained.

Yield: 70%.

G) (S)-(-)-(2-[4-Benzyl-2-(3,4-difluorophenyl)-morpholin-2-yl]-1-ethanol.

(IIIa): X = F, R₁ = -CH₂-; process A, stage a).

6 ml of a 0.5M solution of 9-borabicyclo-[3.3.1]nonane in THF are added under a nitrogen atmosphere to 0.8 g of the compound obtained in the preceding stage, the bulk temperature is brought to 25°C and the mixture is left stirring for 24 hours. 6 ml of THF are added, the reaction mixture is cooled to 0°C, the addition is carried out, in portions of 5 × 0.2 ml, of a solution comprising 1 ml of an 11M solution (130 volumes) of hydrogen peroxide in water and 0.64 g of NaOH pellets, and the mixture is left stirring for 15 minutes at AT. The THF is concentrated under vacuum, the mixture is extracted with 10 ml of toluene, the organic phase is washed with 2 × 10 ml of water and dried over MgSO₄, and the solvent is evaporated under vacuum. The oil obtained is chromatographed on 20 g of silica, elution being carried out with the DCM/diethyl ether (73/3, v/v) mixture. 0.78 g of the expected product is obtained.

Yield: 93%.

H) (S)-(-)-2-[2-(3,4-Difluorophenyl)morpholin-2-yl]-1-ethanol.

(I): X = F; process A, stage b).

The addition is carried out under a nitrogen atmosphere, to 0.078 g of 50% wet 10% palladium-on-

charcoal, of a solution of 0.78 g of the compound obtained in the preceding stage in 10 ml of MeOH and 0.195 ml of concentrated HCl. Hydrogenation is carried out for 2 hours at atmospheric pressure and at AT. The catalyst is filtered off and the filtrate is concentrated under vacuum. 0.5 g of the expected product is obtained.

Yield: 85%.

Enantiomeric purity: 99.95%.

10 EXAMPLE 5 - Synthetic route V.

(S)-(-)-2-[2-(3,4-Difluorophenyl)morpholin-2-yl]-1-ethanol.

(I): X = F.

A) 2-(3,4-Difluorophenyl)-2-hydroxybut-3-enal, single isomer.

This compound is prepared by using the procedures of stages A, B, C and D of EXAMPLE 4.

B) 2-(3,4-Difluorophenyl)but-3-ene-1,2-diol, single isomer.

20 (XX): X = F; process I, stage d).

A solution of 3.2 g of the compound obtained in the preceding stage in 110 ml of toluene is cooled to 0°C and a solution of 0.3 g of sodium borohydride in 10 ml of EtOH is added dropwise. The reaction mixture is hydrolyzed with addition of 100 ml of a saturated NH₄Cl solution, the organic phase, after separating by settling, is washed with 3 × 30 ml of water and dried

over MgSO_4 , and the solvent is evaporated under vacuum.
 The oily residue is chromatographed on silica gel,
 elution being carried out with the DCM/diethyl ether
 (90/10, v/v) mixture. 1 g of the expected product is
 5 obtained.

Yield: 31%.


C) 2-(3,4-Difluorophenyl)-2-vinyloxirane, single
 isomer.

(VII): $X = \text{F}$; process I, stage e).

10 A solution of 1 g of the compound obtained in
 the preceding stage and 0.04 g of benzyltriethyl-
 ammonium chloride in 5 ml of DCM is added to a solution
 of 2 g of NaOH pellets in 2 ml of water and then 0.91 g
 of benzenesulfonyl chloride is run in at AT, the bulk
 15 temperature rising to 35°C . 5 ml of DCM are added and
 the mixture is left stirring for 30 minutes. The
 reaction mixture is hydrolyzed by addition of 20 ml of
 water and diluted with 20 ml of DCM. After separating
 by settling, the organic phase is washed with 4×10 ml
 20 of water and dried over MgSO_4 , and the solvent is
 evaporated under vacuum. 0.91 g of the expected product
 is obtained.

Yield: quantitative.

D) (S)-(-)-1-[Benzyl(2-hydroxyethyl)amino]-2-(3,4-
 25 difluorophenyl)but-3-en-2-ol.

(IVa): $X = \text{F}$, $R_1 = -\text{CH}_2-$  ; process I, stage f).

0.742 g of 2-(benzylamino)-1-ethanol is added to a solution of 0.894 g of the compound obtained in the preceding stage in 4.5 ml of acetonitrile and then the mixture is heated at reflux for 24 hours. The reaction mixture is concentrated under vacuum, the residue is taken up in 20 ml of toluene, and the organic phase is washed with 3 x 10 ml of water, acidified by addition of 20 ml of 0.5N HCl and extracted with 10 ml of water. The acidic aqueous phase is washed with 10 ml of toluene, basified by addition of 0.41 g of NaOH pellets and extracted with 20 ml of toluene, the organic phase is washed with 3 x 10 ml of water and dried over MgSO₄, and the solvent is evaporated under vacuum. 0.99 g of the expected product is obtained.

Yield: 60%.

Enantiomeric purity: 98.8% (e.e. = 97.6%).

E) (S)-(-)-2-[2-(3,4-Difluorophenyl)morpholin-2-yl]-1-ethanol.

(I): X = F; process C and then process A, stages a) and b).

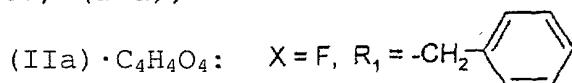
The preparation is carried out as in stages F, G and H of EXAMPLE 4, starting from the compound obtained in the preceding stage, and the expected product is obtained.

EXAMPLE 6 - Synthetic route VI.

(R)-(+)-2-[2-(3,4-Difluorophenyl)morpholin-2-yl]-1-ethanol, salt with L-(-)-di-para-toluoyltartaric acid.

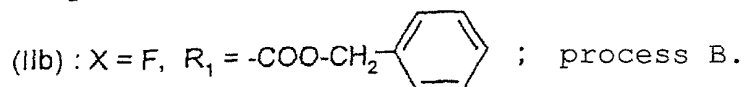
(I): X = F.

- 5 A) 4-Benzyl-2-(3,4-difluorophenyl)-2-vinylmorpholine maleate, (IIa),




This compound is prepared by using the procedures of stages A, B, C and D of example 1.

- B) Benzyl 2-(3,4-difluorophenyl)-2-vinylmorpholine-10 4-carboxylate.



A mixture of 41.98 g of the compound obtained in stage A in the free base form (oil) and 0.55 g of K₂CO₃ is heated to 60°C, 28.68 g of benzyl chloroformate are then added dropwise over 25 minutes under a
15 nitrogen atmosphere, and the mixture is left stirring for 5 hours at 20°C. 100 ml of toluene and 70 ml of water are added to the still hot reaction mixture, then the organic phase, after separating by settling, is washed with water and dried over MgSO₄, and the solvent
20 is concentrated under vacuum. 64 g of the expected product are obtained, which product is used as is in the following stage.

C) Benzyl 2-(3,4-difluorophenyl)-2-(2-hydroxyethyl)-morpholine-4-carboxylate.

(IIIb) : $X = F$, $R_1 = -COO-CH_2-$  ; process A, stage a).

A solution of 6.35 g of trimethylsilyl chloride in 8 ml of THF is added under a nitrogen atmosphere over 15 minutes to a mixture of 2.21 g of sodium borohydride in 50 ml of THF and the mixture is left stirring at AT for 30 minutes. A solution of 7.17 g of the compound obtained in the preceding stage in 11 ml of THF is subsequently added dropwise and the mixture is left stirring at AT for 1 hour, then heated at reflux for 1 hour and left stirring overnight while allowing the temperature to return to AT. 1.05 ml of water are carefully added dropwise to the reaction mixture and then the THF is concentrated under vacuum. The residue is taken up in 60 ml of toluene, 0.24 g of tetrabutylammonium hydrogensulfate is added, 5.4 ml of 10N NaOH are then slowly added and, subsequently, 3.8 ml of an 11M solution of hydrogen peroxide in water (33%, 130 volumes, $d = 1.13$) are added, the bulk temperature reaching 45°C. After stirring for 15 minutes, 60 ml of water are added to the reaction mixture, the organic phase, after separating by settling, is washed twice with water ($pH = 7$) and dried over $MgSO_4$, and the solvent is evaporated under vacuum. 4.83 g of the expected product are obtained, which product is used as is in the following stage.

D) 2-[2-(3,4-Difluorophenyl)morpholin-2-yl]-1-ethanol, racemic.

(I): X = F; process A, stage b).

A solution of 0.77 g of the compound obtained in the preceding stage in 2.3 ml of toluene is added under a nitrogen atmosphere to 0.05 g of 50% wet 10% palladium-on-charcoal. Hydrogenation is carried out for 2 hours 30 minutes at atmospheric pressure and at 40°C. After cooling to AT, water is added to the mixture, and the mixture is acidified by addition of 0.105 ml of concentrated HCl and filtered. After separating by settling, the acidic aqueous phase is washed with toluene, basified by addition of 0.141 ml of 10N NaOH and left stirring at AT for 1 hour. The precipitate formed is filtered off, washed with water and dried under vacuum at 60°C. 0.17 g of the expected product is obtained.

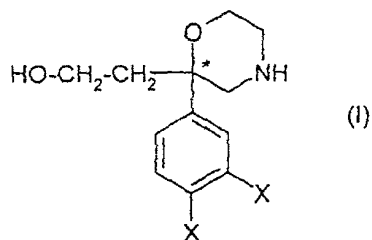
E) (R)-(+)-2-[2-(3,4-Difluorophenyl)morpholin-2-yl]-1-ethanol, salt with L-(-)-di-para-toluoyltartaric acid.

(I): X = F; process A, stage c).

The preparation is carried out as in stage G of EXAMPLE 1, starting from the compound obtained in the preceding stage, and the expected product is obtained.

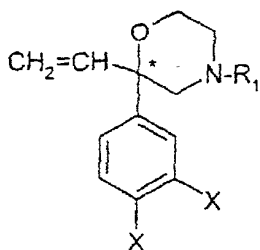
CLAIMS

1. A process for the preparation of a compound, in the enantiomerically pure form, of formula:



in which X represents a halogen atom, of its salts with inorganic or organic acids or of its salts with optically active organic acids, characterized in that:

a) a compound, in the racemic form, in the form of a mixture of diastereoisomers or in the enantiomerically pure form, of formula:



(II): (IIa): $R_1 = -CH_2-$

(IIb): $R_1 = -COO-CH_2-$

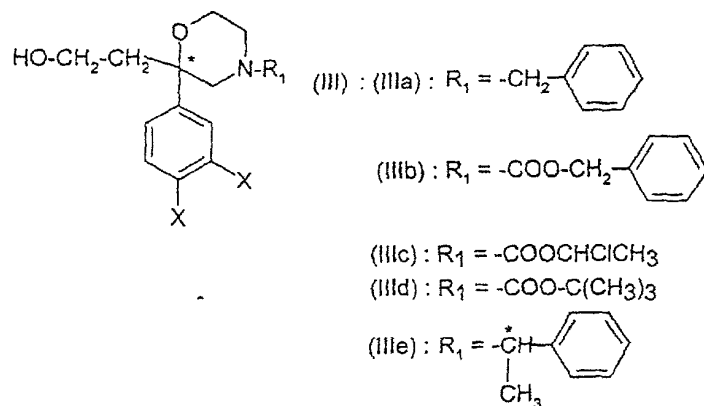
(IIc): $R_1 = -COOCHClCH_3$

(IId): $R_1 = -COO-C(CH_3)_3$

(IIe): $R_1 = -\overset{*}{CH}-$
 $\quad \quad \quad |$
 $\quad \quad \quad CH_3$

in which X is as defined for a compound of formula (I) and R_1 represents an N-protecting group chosen from a benzyl group, a benzyloxycarbonyl group, a 1-chloro-ethyloxycarbonyl group, a *tert*-butyloxycarbonyl group or an α -methylbenzyl group, is converted to a compound,

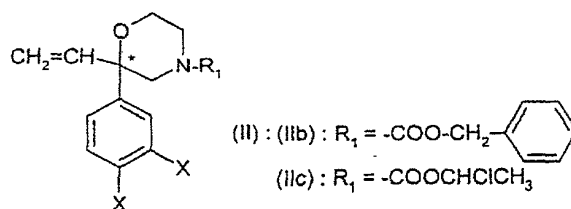
in the racemic form, in the form of a mixture of diastereoisomers or in the enantiomerically pure form, of formula:



5 b) the compound of formula (III) thus obtained is deprotected;

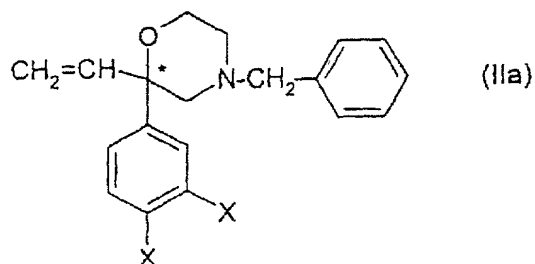
 c) if appropriate, when the compound of formula (I) thus obtained is in the racemic form, the enantiomers are separated, and, optionally, the enantiomerically pure compound of formula (I) is converted to one of its salts with inorganic or organic acids.

2. The process as claimed in claim 1, characterized in that a compound, in the enantiomerically pure form or in the racemic form, of formula:



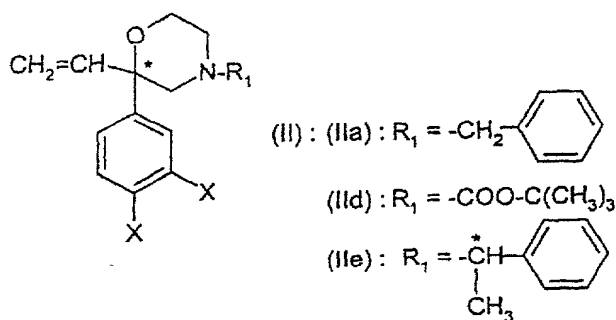
in which X represents a halogen atom and R_1 represents a benzyloxycarbonyl group or a 1-chloroethyloxycarbonyl

group, is prepared by reaction of a compound, in the enantiomerically pure form or in the racemic form, of formula:

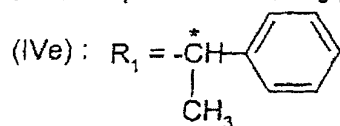


5 in which X is as defined for a compound of formula (II), with benzyl chloroformate or 1-chloroethyl chloroformate in the presence of a base, with or without solvent.

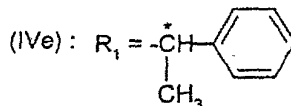
3. The process as claimed in either of
10 claims 1 and 2, characterized in that a compound, in the enantiomerically pure form, in the form of a mixture of diastereoisomers or in the racemic form, of formula:



15 in which X represents a halogen atom and R_1 represents a benzyl group, a *tert*-butyloxycarbonyl group or an α -methylbenzyl group, of its optional salts with inorganic or organic acids, is prepared by cyclization

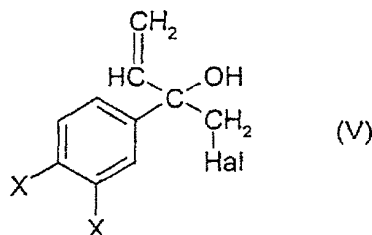
OCCCN(Cc1cc(C=C)c(C)c1)C(O)C

4. The process as claimed in claim 3, characterized in that a compound, in the

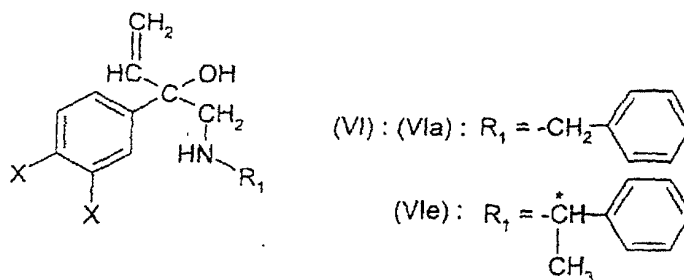
*C(O)(CN(CO)CO)C(=O)C=Cc1cc(X)cc(X)c1

in which X represents a halogen atom and R₁ represents a benzyl group or an α-methylbenzyl group, of its salts with inorganic or organic acids, is prepared:

a) by reaction of a compound, in the racemic form, of formula:



in which X is as defined for a compound of formula (IV)
 5 and Hal represents a halogen atom, with benzylamine or
 with R-(+)- or S-(-)- α -methylbenzylamine in the
 presence of a base in an inert solvent, to produce a
 compound, in the racemic form, of formula:



10

b) by separation of the enantiomers or
 diastereoisomers of the compound of formula (VI) thus
 obtained;

c) by reaction of the enantiomerically pure
 15 compound of formula (VI) thus obtained:

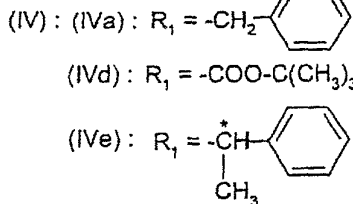
- either with ethylene oxide in the catalytic
 presence of an acid in an inert solvent;

- or with a compound of formula $Hal'''-CH_2-CH_2-O-R_2$
 (XXI), in which R_2 represents an O-protecting group and
 20 Hal''' represents a halogen atom, in the presence of a

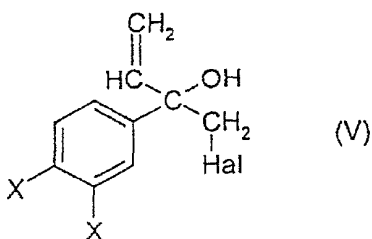
and, optionally, by conversion of the enantiomerically pure compound of formula (IV) thus

5. The process as claimed in claim 4, characterized in that, in stage a), use is made of a compound of formula (V) in which Hal represents a chlorine or bromine atom.

15

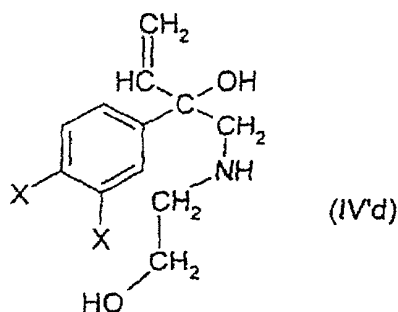


a) by reaction of a compound, in the racemic form, of formula:



in which X is as defined for a compound of formula (IV) and Hal represents a halogen atom, either with 2-(benzylamino)-1-ethanol or with 2-amino-1-ethanol or with (R)- or (S)-2-(α -methylbenzylamino)-1-ethanol, in the presence of a base and in an inert solvent, and, optionally, by conversion of the compound of formula (IVa) or (IVe) thus obtained to one of its salts with inorganic or organic acids;

- 10 b) if appropriate, when the compound of formula (V) is employed with 2-amino-1-ethanol in stage a), by reaction of the compound thus obtained, of formula:

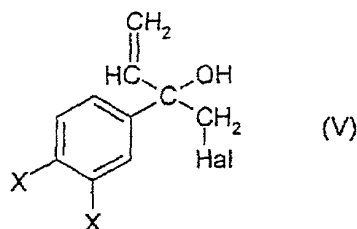


- 15 with di-*tert*-butyl dicarbonate in the presence of a base and in an inert solvent, to produce the compound of formula (IVd).

7. The process as claimed in claim 6, characterized in that use is made of a compound of

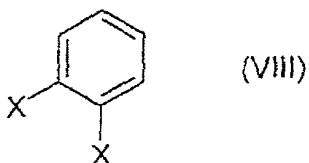
formula (V) in which Hal represents a chlorine or bromine atom.

8. The process as claimed in either of claims 4 and 6, characterized in that a compound of formula:



in which X represents a halogen atom and Hal represents a halogen atom, is prepared:

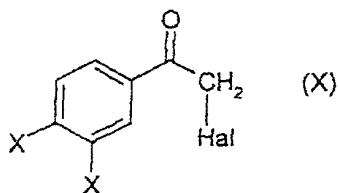
a) by reaction of a compound of formula:



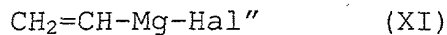
in which X is as defined for a compound of formula (V), with a compound of formula:

Hal'-CO-CH₂-Hal (IX)

in which Hal' and Hal represent a halogen atom, in the presence of a Lewis acid and in an inert solvent, to produce a compound of formula:



b) by reaction of the compound of formula (X) thus obtained with a compound of formula:

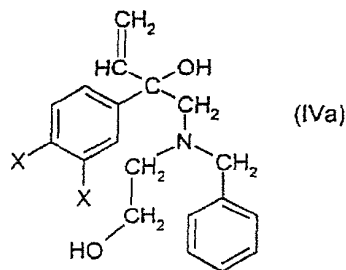


in which Hal'' represents a halogen atom, in an inert solvent, followed by hydrolysis, to produce the compound of formula (V).

9. The process as claimed in claim 8, characterized in that a compound of formula (V) in which Hal represents a chlorine or bromine atom is prepared.

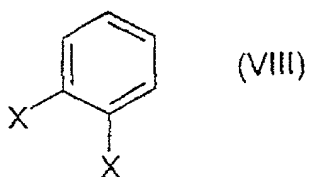
10. The process as claimed in claim 8, characterized in that, in stage a), use is made of a compound of formula (IX) in which Hal' and Hal each independently represent a chlorine or bromine atom and, in stage b), use is made of a compound of formula (XI) in which Hal'' represents a chlorine or bromine atom.

11. The process as claimed in claim 3, characterized in that a compound, in the racemic form, of formula:

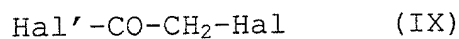


in which X represents a halogen atom, or one of its salts with inorganic or organic acids, is prepared:

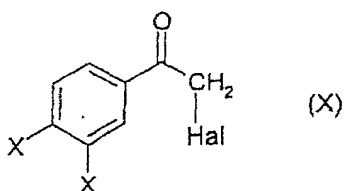
a) by reaction of a compound of formula:



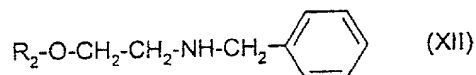
in which X is as defined for a compound of formula (IVa), with a compound of formula:



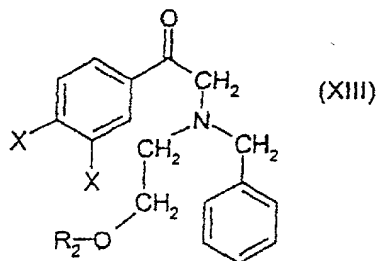
- 5 in which Hal' and Hal represent a halogen atom, in the presence of a Lewis acid and in an inert solvent, to produce a compound of formula:



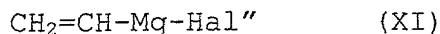
- 10 b) by reaction of the compound of formula (X) thus obtained with a compound of formula:



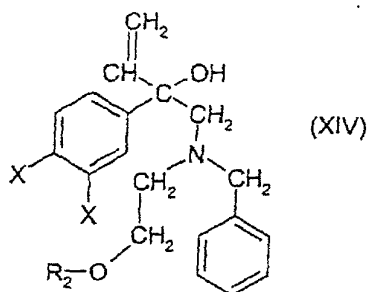
- 15 in which R₂ represents an O-protecting group, in the presence of a base and in an inert solvent, to produce a compound of formula:



- c) by reaction of the compound of formula (XIII) thus obtained with a compound of formula:



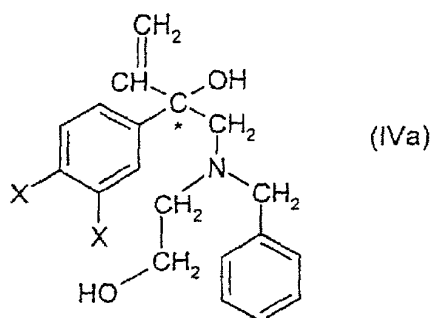
in which Hal'' represents a halogen atom, in an inert solvent, followed by hydrolysis, to produce a compound of formula:



d) by deprotection of the compound of formula (XIV) and, optionally, by conversion of the compound of formula (IVa) thus obtained to one of its salts with inorganic or organic acids.

12. The process as claimed in claim 11, characterized in that, in stage a), use is made of a compound of formula (IX) in which Hal and Hal' each independently represent a chlorine or bromine atom, in stage b), use is made of a compound of formula (XII) in which R₂ represents a tetrahydropyran-2-yl group, and, in stage c), use is made of a compound of formula (XI) in which Hal'' represents a chlorine or bromine atom.

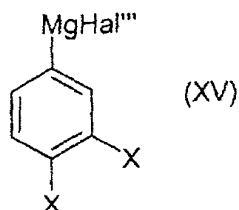
13. The process as claimed in claim 3, characterized in that a compound, in the enantiomerically pure form, of formula:



in which X represents a halogen atom, or one of its salts with inorganic or organic acids, is prepared:

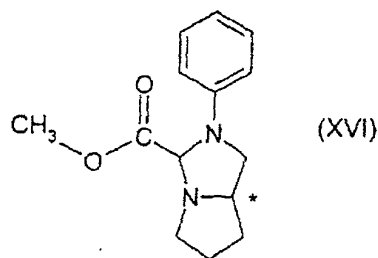
a) by reaction of a compound of formula:

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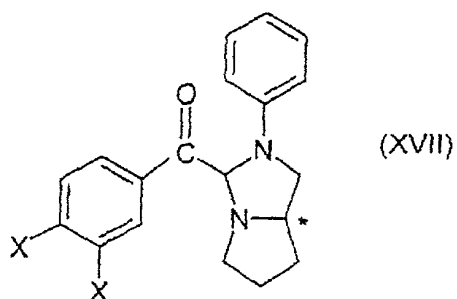


in which X is as defined for a compound of formula (IVa) and Hal''' represents a halogen atom, with methyl (R)- or (S)-2-phenylhexahydropyrrolo[1,2-c]imidazole-3-

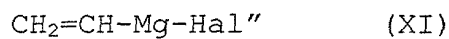
10 carboxylate, of formula:



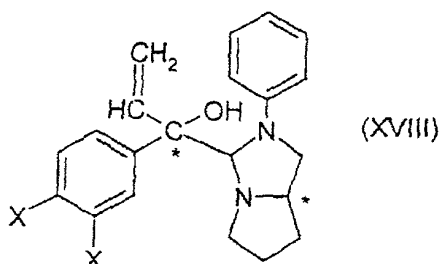
in the presence of magnesium chloride in an inert solvent, followed by hydrolysis, to produce a compound, in the enantiomerically pure form, of formula:



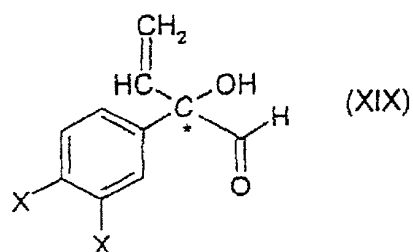
b) by reaction of the compound of formula (XVII) thus obtained with a compound of formula:



5 in which Hal'' represents a halogen atom, in an inert solvent, followed by hydrolysis, to produce a compound, in the enantiomerically pure form, of formula:

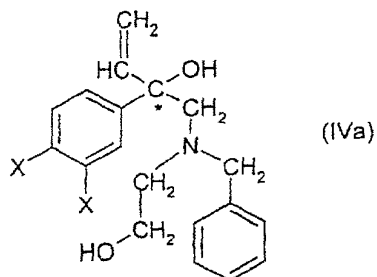


c) by hydrolysis of the compound of formula
10 (XVIII) thus obtained by the action of an acid in an inert solvent as a mixture with water, to produce a compound, in the enantiomerically pure form, of formula:



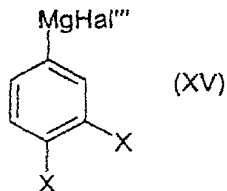
d) by reaction of the compound of formula (XIX) thus obtained with 2-(benzylamino)-1-ethanol in the presence of an acid in an inert solvent, then reduction of the iminium salt formed as an intermediate by means of a reducing agent and, optionally, conversion of the enantiomerically pure compound of formula (IVa) to one of its salts with inorganic or organic acids.

14. The process as claimed in claim 3, characterized in that a compound, in the enantiomerically pure form, of formula:

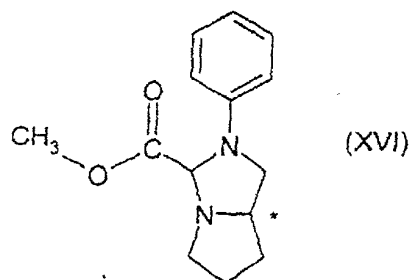


in which X represents a halogen atom, or one of its salts with inorganic or organic acids, is prepared:

a) by reaction of a compound of formula:

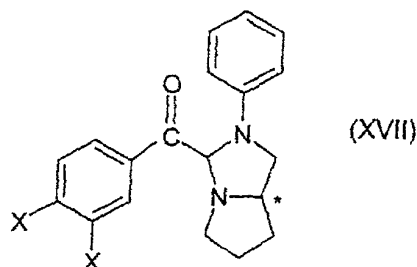


in which X is as defined for a compound of formula (IVa) and Hal''' represents a halogen atom, with methyl (R)- or (S)-2-phenylhexahydropyrrolo[1,2-c]imidazole-3-carboxylate, of formula:

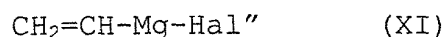


in the presence of magnesium chloride in an inert solvent, followed by hydrolysis, to produce a compound, in the enantiomerically pure form, of formula:

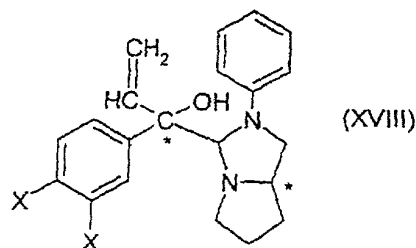
5



b) by reaction of the compound of formula (XVII) thus obtained with a compound of formula:

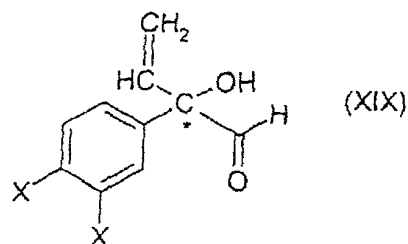


10 in which Hal'' represents a halogen atom, in an inert solvent, followed by hydrolysis, to produce a compound, in the enantiomerically pure form, of formula:

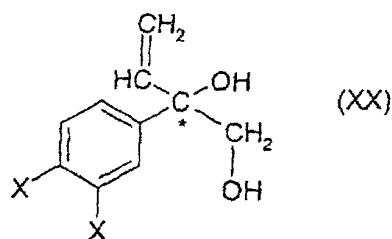


c) by hydrolysis of the compound of formula
15 (XVIII) thus obtained by the action of an acid in an inert solvent as a mixture with water, to produce a

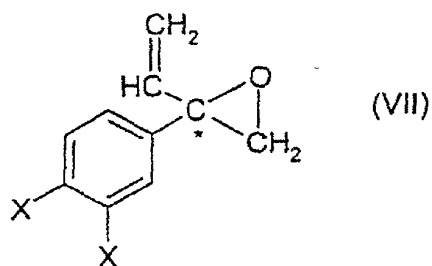
compound, in the enantiomerically pure form, of formula:



- 5 d) by reduction of the compound of formula (XIX) thus obtained by means of a reducing agent in an inert solvent, to produce a compound of formula:



- 10 e) by cyclization of the compound of formula (XX) thus obtained, to produce a compound, in the enantiomerically pure form, of formula:



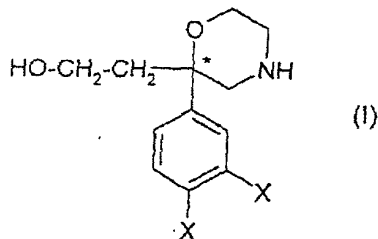
- f) by reaction of the compound of formula (VII) thus obtained with 2-(benzylamino)-1-ethanol in the presence of a base and in an inert solvent and, optionally, conversion of the enantiomerically pure
- 15

compound of formula (IVa) thus obtained to one of its salts with inorganic or organic acids.

15. The process as claimed in either of claims 13 and 14, characterized in that, in stage a), use is made of a compound of formula (XV) in which Hal^{'''} represents a chlorine or bromine atom and, in stage b), use is made of a compound of formula (XI) in which Hal^{''} represents a chlorine or bromine atom.

16. The process as claimed in one of claims 1, 2, 3, 4, 6, 8, 11, 13 and 14, characterized in that compounds of formula (I), (IIa), (IIb), (IIc), (IId), (IIe), (IVa), (IVd), (IVe) or (V) in which X represent a chlorine atom or a fluorine atom are prepared.

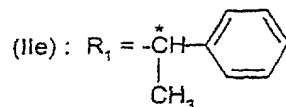
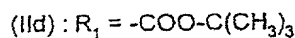
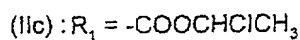
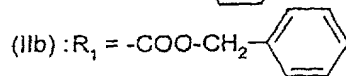
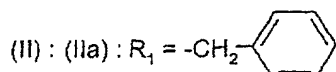
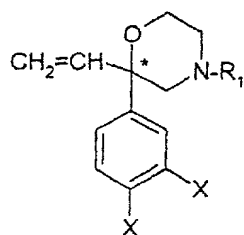
17. An enantiomerically pure compound of formula:



in which X represents a halogen atom, in the form of an optically active salt with optically active organic acids.

18. The compound as claimed in claim 17, in the form of the salt with L-(-)- or D-(+)-di-para-toluoyltartaric acid.

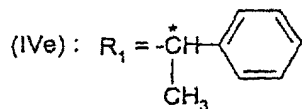
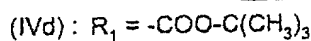
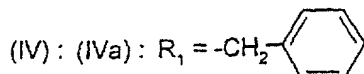
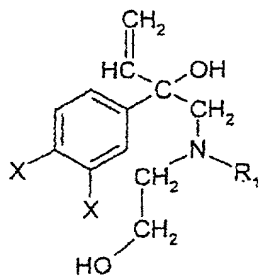
19. A compound of formula:



in which X represents a halogen atom and R_1 represents an N-protecting group chosen from a benzyl group, a benzyloxycarbonyl group, a 1-chloroethyloxycarbonyl group, a *tert*-butyloxycarbonyl group or an α -methylbenzyl group, in the racemic form, in the enantiomerically pure form or in the form of a mixture of diastereoisomers, and its optional salts with inorganic or organic acids.

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20. A compound of formula:



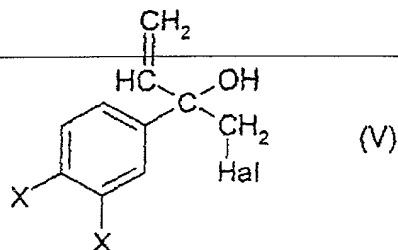
in which X represents a halogen atom and R_1 represents a benzyl group, a *tert*-butyloxycarbonyl group or an α -methylbenzyl group, in the racemic form, in the

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enantiomerically pure form or in the form of a mixture of diastereoisomers, and its optional salts with inorganic or organic acids.

21. A compound of formula:

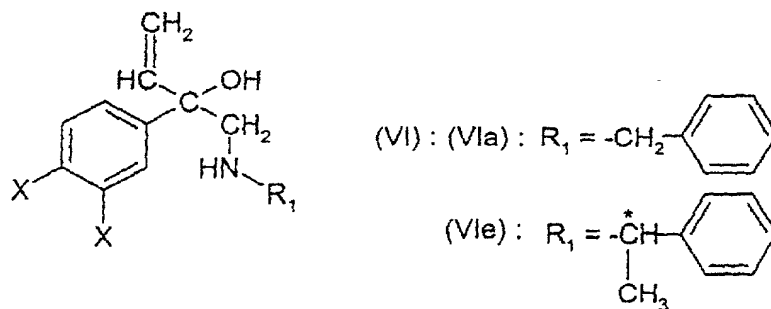
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in which X represents a halogen atom and Hal represents a halogen atom.

22. The compound as claimed in claim 21 of formula (V), in which Hal represents a chlorine or bromine atom.

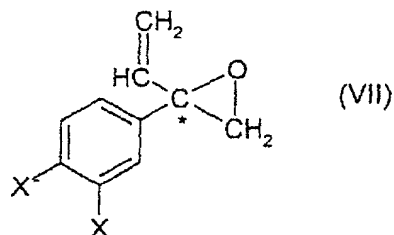
23. A compound of formula:



15 in which X represents a halogen atom and R_1 represents a benzyl group or an α -methylbenzyl group, in the racemic form, in the enantiomerically pure form or in the form of a mixture of diastereoisomers, and its salts with inorganic or organic acids or its salts with optically
 20 active acids.

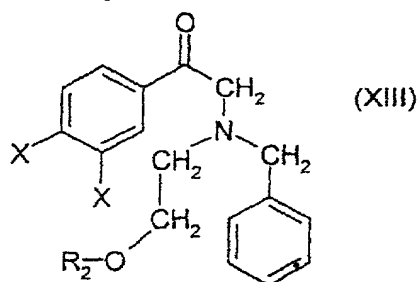
24. The enantiomerically pure compound of formula (VIa) as claimed in claim 23, in the form of the salt with L-(+)- or D-(-)-mandelic acid.

25. A compound of formula:



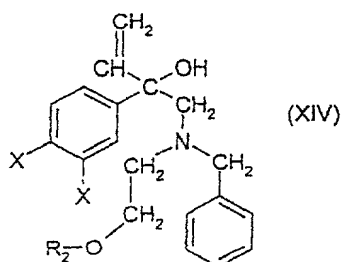
in which X represents a halogen atom, in the racemic form or in the enantiomerically pure form.

26. A compound of formula:



in which X represents a halogen atom and R₂ represents an O-protecting group, and its salts with inorganic or organic acids.

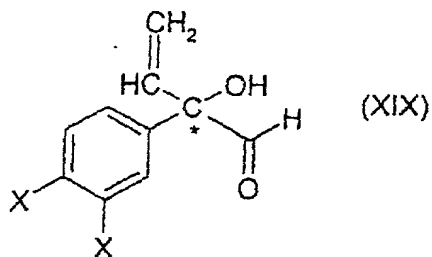
27. A compound of formula:



in which X represents a halogen atom and R₂ represents an O-protecting group, and its salts with inorganic or organic acids.

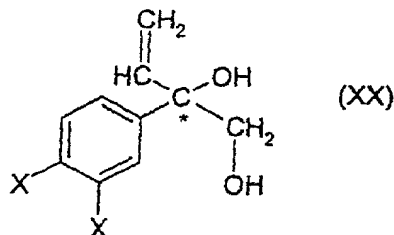
28. The compound as claimed in claim 26 or 27 of formula (XIII) or (XIV), in which R₂ represents a tetrahydropyran-2-yl group.

29. A compound of formula:



in which X represents a halogen atom, in the racemic form or in the enantiomerically pure form.

30. A compound of formula:



in which X represents a halogen atom, in the racemic form or in the enantiomerically pure form.

31. The compound as claimed in one of claims 17 to 30 of formula (I), (II), (IV), (V), (VI), (VII), (XIII), (XIV), (XIX) or (XX) in which X represents a chlorine atom or a fluorine atom.

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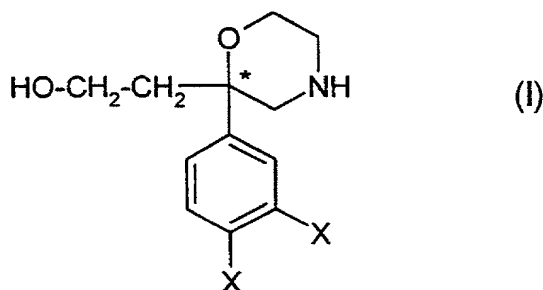
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[Suite sur la page suivante]

(54) Title: METHOD FOR PREPARING 2-(2-ARYLMORPHOLIN-2-YL)ETHANOL DERIVATIVES AND INTERMEDIATES

(54) Titre: PREPARATION DE DERIVES DE 2-(2-ARYLMORPHOLIN-2-YL)ETHANOL ET INTERMEDIAIRES



(57) Abstract: The invention concerns novel methods for preparing enantiopure compounds of formula (I) wherein X represents a halogen atom, its additive salts with mineral or organic acids, or its salts with optically active organic acids. The invention also concerns intermediate compounds of formulae (II), (IV), (V), (VI), (VII), (XIII), (XIV), (XIX) and (XX). The invention further concerns enantiomerically pure compounds of formula (I), in the form of optically active salt with optically active organic acids.

(57) Abrégé: L'invention concerne de nouveaux procédés de préparation de composés, sous forme énantiomériquement pure, de formule (I), dans laquelle X représente un atome d'halogène, de ses sels avec des acides minéraux ou organiques, ou de ses sels avec des acides organiques optiquement actifs. L'invention a aussi pour objet les composés intermédiaires de formule (II), (IV), (V), (VI), (VII), (XIII), (XIV), (XIX) ET (XX). L'invention concerne enfin les composés de formule (I), énantiomériquement purs, sous forme de sel optiquement actif avec des acides organiques optiquement actifs.

WO 01/04105 A1

Page 1 of 3

I/We hereby claim benefit under Section 119(e) of Title 35 of the United States Code of any United States provisional application(s) identified below:

Application No. Filing Date

I/We hereby claim benefit under Section 120 of Title 35 of the United States Code of any United States application(s) or PCT international application(s) designating the United States identified below:

Application Serial No. Filing Date Status

I/We hereby appoint Michael D. Alexander, Reg. No. 36,080; and Paul E. Dupont, Reg. No. 27,438, or any of them my/our attorneys or agents with full power of substitution and revocation to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith.

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Telephone No. _____

I/We hereby declare that all statements made herein and in the above-identified application of my/our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Inventor's signature

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500 Full name of fifth joint inventor

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600 Full name of sixth joint inventor

LUCAS Eric

Inventor's signature

Lucas

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